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APPLICATION NUMBER:

761029Orig1s000

MEDICAL REVIEW(S)

Clinical Review

Maria Lourdes Villalba, M.D.

BLA 761029

BLA 761029 Daclizumab High Yield Process (Zinbryta)

Amendment to Safety Review dated March 24, 2016, Reference ID: 3906449.

Reviewer: Maria Lourdes Villalba, M.D.
Medical Officer, Division of Neurology Products, Safety Team

The following corrections are made to the above referenced document:

1. Daclizumab High Yield Process is a 351(a) Biologic application, not a New Molecular Entity.
2. Patient 302/512-103 is incorrectly referred to as 203/512-103 in Table 13.3.4.1, Listing of serious DILI (Page 248). The total number of cases of serious DILI in the Total DAC HYP database is 20 instead of 21 (the percentage is the same [0.9%]). This correction should be applied throughout the review.
3. The patients on DAC150 who had a liver biopsy in study 301 are 301/624-012 and 301/670-035). Three (instead of five) patients were treated with high dose corticosteroids for suspected AIH in study 301 (301/453-041, 301/670-024, and 301/670-035). (Page 129 of the review).
4. Correct citation for anti-Smooth muscle (ASMA) antibody reference values and interpretation in Page 258 of the review is Michael Heneghan, Autoimmune hepatitis: Serologic markers. UpToDate®, Topic 3628 Version 17.0.
5. In Page 311 of the review, patient 203/555-001 with recent diagnosis of sarcoidosis and angioedema was listed twice and patient 303/325-001* with renal sarcoidosis was omitted. The total number of reports of sarcoidosis is still nine.
6. Patient 301/512-006 is said to have had eosinophilia and slight pancreatitis in several sections of the review. This patient did not have eosinophilia or pancreatitis.
7. The rate of potential immune mediated reactions in the Total DAC HYP database using a customized MedDRA Query is 28%. (Pages 196 and 202 and Page 212 of the review.)

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

MARIA L VILLALBA
05/27/2016

SALLY U YASUDA
05/27/2016

Safety Team Leader Review

Date	May 26, 2016
From	Sally Usdin Yasuda
Subject	Safety Team Leader Review
NDA/BLA #	BLA 761029
Supplement#	
Applicant	Biogen
Date of Submission	February 27, 2015
PDUFA Goal Date	May 27, 2016 (extended clock)
Proprietary Name / Non-Proprietary Name	Zinbryta/Daclizumab
Dosage form(s) / Strength(s)	Solution for subcutaneous injection, 150 mg/ml
Applicant Proposed Indication(s)/Population(s)	Relapsing forms of Multiple Sclerosis, Adult Population
Recommendation on Regulatory Action	If efficacy is demonstrated and the benefits of daclizumab outweigh the risks, then I recommend that approval include a REMS with ETASU, labeling language including a boxed warning, recommendations for stringent monitoring and evaluation, and a medication guide to mitigate the risks.
Recommended Indication(s)/Population(s) (if applicable)	

1. Benefit-Risk Assessment

Benefit-Risk Summary and Assessment

Daclizumab (DAC) is proposed to be used for treatment of adults with relapsing forms of multiple sclerosis (RMS). This review evaluates the safety of DAC. If efficacy is demonstrated and the benefits of DAC outweigh the risks, then I recommend that approval be accompanied by labeling language including a boxed warning and a medication guide to mitigate the risks. I also agree with establishment of a Risk Evaluation and Mitigation Strategy (REMS).

This document reviews the risk profile of DAC. I summarize the findings of Dr. Lourdes Villalba. DAC causes serious and life-threatening adverse reactions, including life-threatening liver injury. These adverse reactions will not be completely prevented even with stringent risk mitigation strategies, and it is likely that deaths, including deaths due to liver injury, would occur postmarketing. Based on safety findings, Dr. Villalba does not recommend approval for DAC. Neither does Dr. John Senior who provided a consult regarding hepatotoxicity. However, a recommendation regarding approvability can only be made based on a consideration of benefit and risk. I will provide an assessment of the risk, and recommendations for labeling and strategies to mitigate the risk if efficacy is demonstrated and it is determined that the benefits outweigh the risk such that DAC would be approved. If DAC can be approved, limiting its use to a subset of patients with the most favorable benefit to risk ratio may be appropriate.

Risk:

DAC is associated with severe and potentially life-threatening adverse effects. One death occurred in a patient with autoimmune hepatitis likely caused by DAC. DAC causes potentially fatal hepatic injury, severe autoimmune and other immune conditions, dermatologic reactions, infections, and lymphadenopathy. Depression occurred more frequently in DAC-treated subjects than in interferon beta-1a-treated subjects and serious events of depression and suicidality occurred slightly less (0.4% of DAC vs 0.7% of Avonex) than in interferon beta-1a that has a Warning for Depression and Suicide. Breast cancer occurred at rates greater than background in the general population. Acute hypersensitivity and multiorgan hypersensitivity and multiorgan failure also occurred in subjects treated with DAC. Onset of events was unpredictable, occurred throughout the course of therapy and even after DAC was discontinued, some resolved months after DAC was discontinued or did not resolve through the follow-up period, and some required invasive procedures to diagnose, hospitalization, and, blood transfusions, systemic steroids and other immunosuppressive medications to treat. There is uncertainty regarding whether patients and physicians would be adherent to labeling recommendations regarding monitoring and evaluation of liver laboratory values prior to the next dose. However, a strongly worded boxed warning, information about monitoring in Section 2 of the label, Warnings, and a medication guide would provide guidance. Labeling would require a boxed warning at least for DILI and would include recommendations for monitoring and evaluation of liver laboratory values and for initiating, interrupting, and stopping DAC when appropriate. Labeling would also require warnings for other events listed above. I agree that the labeling should be supported by a REMS with ETASU.

Paragraph #5: Analysis and Recommendation with Respect to Safety:

If DAC is approved, I recommend a Boxed Warning for DILI and for immune-mediated reactions, and recommendations in Section 2 of labeling for monitoring and evaluation of liver laboratory values before initiating DAC and prior to the next dose, with recommendations for treatment interruption and discontinuation. I recommend contraindications for use in patients with pre-existing hepatic disease or hepatic impairment. I recommend a Medication Guide to describe these risks and symptoms of concern, and to highlight the need for monitoring, evaluation, and prompt medical attention should specific adverse events occur. I agree with a REMS with ETASU to address the risks of DILI and serious daclizumab-induced autoimmune disease. I recommend the following postmarketing requirements:

- Long-term observational registry study to further characterize the risk of DILI and other serious risks including malignancy, serious skin reactions, and other immune and autoimmune conditions
- Clinical study to identify biomarkers to predict patients at risk for DILI, serious skin reactions, and daclizumab-induced autoimmune disorders.
- Pregnancy registry.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
<u>Analysis of Condition</u>	<ul style="list-style-type: none"> • Please refer to Dr. Rodichok’s review of clinical efficacy. 	
<u>Current Treatment Options</u>	<ul style="list-style-type: none"> • Please refer to Dr. Rodichok’s review of clinical efficacy. 	
<u>Benefit</u>	<ul style="list-style-type: none"> • Please refer to Dr. Rodichok’s review of clinical efficacy. 	

Dimension	Evidence and Uncertainties	Conclusions and Reasons
<p>Risk</p>	<p><u>Safety database</u> The safety database for DAC includes 3 clinical trials in adults in RMS: Phase 2 placebo controlled study (201), Phase 3 active controlled study (301), their extensions, and Phase 3 open label study (302). Drug exposure is adequate and reflects the intended population for use.</p> <p><u>Safety concerns</u></p> <ul style="list-style-type: none"> • The most common AEs (at least 5% and at least 2% greater than placebo) were: Upper Respiratory Tract Infection (URI, 9%), Depression/Depressed Mood (7%), Rash (7%), and ALT increased (5%). The most common AEs (at least 5% and at least 2% greater than Interferon beta-1a) were: Nasopharyngitis (25%), URI (16%), Dermatitis and Eczema-related Terms (14%), Rashes (10%), Depression/Depressed Mood (10%), Influenza (9%), Oropharyngeal Pain (8%), Bronchitis (7%), and Lymphadenopathy (5%). • Five deaths occurred in DAC-treated subjects: 1 of autoimmune hepatitis, 1 of complications subsequent to a severe cutaneous reaction, both likely related to DAC use; 2 of complications subsequent to aspiration pneumonia in patients with advanced MS, for which a role for DAC in increasing the risk of infection cannot be ruled out; and 1 of subdural and subarachnoid hemorrhage in an anticoagulated patient after a fall. • Serious drug-induced liver injury (DILI), including 1 death, occurred in 20 DAC subjects (0.9%). SAEs of DILI (including liver failure) and transaminase elevations occurred more frequently in DAC than in placebo or interferon beta-1a in controlled trials. Seven DAC subjects had autoimmune hepatitis and 4 subjects had transaminase and bilirubin elevations in the Hy's law range (including 2 of the patients with autoimmune hepatitis) for which a role for DAC cannot be ruled out. Onset of DILI is unpredictable, it occurs despite monitoring, it can be fatal, and risk factors to predict patients who are susceptible are not yet identified. Serious DILI occurred despite stringent monitoring and a requirement to review liver lab values prior to the next dose. 	<p>Major and potentially life-threatening safety issues of drug-induced liver disease (DILI), autoimmune and other serious immune-mediated disease including serious non-infectious colitis, dermatologic disorders, acute hypersensitivity reactions, multiorgan hypersensitivity reactions, infections, depression and suicidality, breast cancer, and lymphadenopathy, occur at the proposed dose of daclizumab. These adverse reactions generally occurred at least as frequently in DAC treated subjects as in interferon beta-1a-treated subjects. Onset of events was unpredictable, occurred throughout the course of therapy and even after DAC was discontinued, some resolved months after DAC was discontinued or did not resolve, and some required invasive procedures to diagnose, hospitalization, and, blood transfusions, systemic steroids and other immunosuppressive medications to treat.</p> <p>Labeling would require a boxed warning for DILI and for immune-mediated reactions with recommendations for monitoring and stopping DAC when appropriate provided in the labeling. Labeling would also require warnings for other events listed above.</p> <p>Monitoring, evaluation, and appropriate discontinuation of DAC can mitigate but not completely prevent the adverse reactions. The magnitude of the potential for serious harm</p>

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	<ul style="list-style-type: none"> • DAC associated immune-mediated adverse events affecting most organ systems occurred in at least 28% of DAC-treated subjects overall. In addition to autoimmune hepatitis and skin conditions including eczema and other dermatitis these included psoriatic conditions in 2%, enteropathy (1.2%), immune-mediated hepatitis (0.3%), sarcoidosis (0.3%), vasculitis (0.3%), celiac disease (0.2%) as well as glomerulonephritis in 2 subjects (< 0.1%), autoimmune hemolytic anemia in 3 subjects (0.1%). Non-infectious colitis-related events occurred in 1.5% of DAC treated subjects (of which 0.3% were SAEs) and none of the interferon beta-1a-treated subjects in Study 301. Sometimes the events presented concurrently or sequentially in the same patient. • Dermatologic reactions occurred more frequently in DAC than in control in the controlled trials; overall, TEAEs in this SOC occurred in 40% of DAC-treated subjects. The events ranged from mild to severe and life-threatening reactions, some requiring treatment with systemic steroids, and some that required months to resolve after discontinuing DAC. The Sponsor has not evaluated whether a biomarker can predict patients at risk for serious skin reactions. • Acute hypersensitivity included angioedema (3.6% in Total DAC; 2.4% on DAC vs 1.2% on Interferon beta-1a in Study 301), anaphylaxis, and serious urticaria. Acute hypersensitivity events occurred throughout the time period of treatment with DAC and lasted up to at least 201 days. • Three subjects had a rash with involvement of other organs or blood count abnormalities such as eosinophilia and at least 5 others had multiorgan failure that may have been immune-mediated. • Serious infections occurred in 4.4% of subjects in Total DAC. SAEs occurred more frequently in DAC than in control in the controlled trials. TEAEs in this SOC occurred slightly more frequently in DAC than in control. SAEs included bacterial, viral, and mycobacterial infections. • SAEs of Depression and Suicide attempt occurred in 6 subjects (0.3%) and 5 subjects (0.2%), respectively. There was no imbalance in 	<p>after approval is unknown. Adherence to monthly monitoring and evaluation particularly of liver transaminases prior to administration of the next dose is necessary. Some reactions require a specialist to diagnose, because the actions taken with the drug, the urgency of the situation, and the treatment required depend on the type of reaction and failure to adequately monitor, recognize signs and symptoms, and provide prompt medical treatment for many adverse reactions in the postmarketing setting would increase the risk of adverse and potentially life-threatening outcomes.</p> <p>For comparison, I show Warnings for other approved MS drugs with similar adverse reactions:</p> <p><u>Hepatic Injury</u>: Tysabri (acute liver failure requiring transplant), Avonex (severe hepatic injury including cases of hepatic failure; autoimmune hepatitis), Gilenya (increased transaminases), Aubagio (boxed warning primarily based on leflunomide).</p> <p><u>Cutaneous Reactions</u>: Aubagio (SJS/TEN for leflunomide)</p> <p><u>Acute Hypersensitivity</u>: Tysabri (including anaphylaxis), Avonex (includes anaphylaxis), Lemtrada (serious infusion reactions in 3% including anaphylactic shock and angioedema), Tecfidera (anaphylaxis and angioedema), Gilenya (including angioedema)</p> <p><u>Immune System</u>: Avonex (autoimmune disorders), Lemtrada (autoimmunity including</p>

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	<p>psychiatric SAEs in controlled studies; in Study 301 SAEs of completed suicide/depression/depression suicidal/suicide ideation/suicide attempt were reported in 0.4% in DAC and 0.7% in interferon beta-1a. Most of the SAEs were in patients with a prior history of depression. TEAEs of Depression/Depressed Mood occurred in 10% of subjects on DAC in Study 301, more frequently than on interferon beta-1a.</p> <ul style="list-style-type: none"> • Seizure SAEs occurred in 0.7% of DAC and 0.2% of interferon beta-1a subjects in Study 301; TEAEs of seizures occurred in 1.2% of DAC subjects and 0.3% of interferon beta-1a subjects. Interferon beta-1a (Avonex) has a Warning in labeling regarding seizures. • Malignancies of breast cancer in women (1 in Study 301 and 7 in extension studies; all in European women) and breast cancer in men (1), occurred in subjects treated with DAC. All occurred at rates greater than reported background rates in the general population. Without a comparator for the cases in the Total DAC database, it is difficult to characterize the risk from DAC. • Lymphadenopathy occurred in 6% of the Total DAC pool and SAEs occurred in 1.6%. There was an imbalance in SAEs and TEAEs for DAC compared to interferon beta-1a in Study 301 but no imbalance in Study 201, reflecting the longer duration of exposure in Study 301. Lymphadenopathy was associated with variety of conditions from mild to serious processes requiring and treatment and invasive procedures to diagnose. <p><u>Safety in the post-market setting</u></p> <ul style="list-style-type: none"> • The sponsor proposes that patients will self-administer DAC compared to clinical trials where DAC was administered by a health care provider (with protocols amended so that administration of the next dose was to occur after review of liver laboratory values). • Whether patients and physicians will adhere to stringent monitoring recommendations, including evaluation of laboratory values, once DAC is marketed is an uncertainty. • Fatal autoimmune hepatitis occurred in a patient who resumed DAC after a 6-month treatment free period. The risk of severe or life- 	<p>thyroid in 34%, immune thrombocytopenia in 2%, glomerulonephropathies in 0.3%).</p> <p><u>Infections:</u> Tysabri (PML, herpes encephalitis and meningitis), Lemtrada (Infections in 71% vs 53% in interferon beta-1a; serious in 3% vs 1% in Avonex), Gilenya (infections in Section 5.2 including life-threatening herpetic infections, Kaposi’s sarcoma, cryptococcal infections; PML in Section 5.3)</p> <p><u>Malignancies:</u> Lemtrada (thyroid cancer [0.3%], melanoma [0.3%]), Gilenya (basal cell carcinoma)</p> <p><u>Depression:</u> Avonex (Section 5.1, depression and suicide)</p> <p><u>Seizures:</u> Avonex (seizures occurred in clinical trials)</p>

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	<p>threatening reactions including autoimmune reactions when resuming DAC after treatment interruption is an uncertainty.</p>	
<p><u>Risk Management</u></p>	<ul style="list-style-type: none"> • A patient registry that will be part of the REMS could be used to support a post-marketing requirement to evaluate the main safety risks of DAC in the postmarketing setting. • Strong product labeling including a boxed warning and a Medication Guide with recommendations for monitoring and evaluation of laboratory parameters is necessary to mitigate the risks of hepatotoxicity and some of the autoimmune/immune mediated reactions. However, even with adequate monitoring, some patients will likely experience serious adverse events. A REMS with ETASU could help support the labeling recommendations. 	<p>A patient registry supporting the post-marketing requirement for an observational safety study will help to evaluate the main safety risks of DAC in the post-marketing setting.</p> <p>A boxed warning should be included in labeling to describe the risks of at least hepatotoxicity and to provide recommendations for monitoring and evaluation of laboratory parameters that require interruption or discontinuation of DAC. A medication guide should be required to describe these risks and symptoms of concern, and to highlight the need for monitoring and evaluation prompt medical attention should specific adverse events occur. A REMS with ETASU could help support the labeling recommendations.</p>

2. Background

This memorandum summarizes the primary concerns from the safety review, conducted by Dr. Lourdes Villalba, of the daclizumab High Yield Process (HYP) BLA 761029 and provides my conclusions and recommendations regarding the safety findings and management of the risks. I also discuss the reviews from Dr. Mark Avigan and Dr. John Senior, Office of Pharmacovigilance and Epidemiology who reviewed hepatotoxicity with daclizumab HYP (DAC) in response to a consult request. In addition, I include the recommendations from the consult of Dr. Amy Rosenberg, Director, Office of Biotechnology Products, Division of Biotechnology Review and Research III, regarding potential biomarkers for identification of patients at risk of DAC-induced autoimmune disease.

- *The product information and the applicant's proposals*

DAC is a humanized monoclonal IgG1 antibody that, according to the sponsor, binds to the alpha subunit of the high-affinity interleukin 2 (IL-2) receptor on T cells (CD25), modulating T cell signaling. The sponsor states that this results in higher levels of IL-2 available for signaling through the intermediate-affinity IL-2 receptor. The sponsor states that DAC reduces regulatory T cells (T regs), but states that there is functional adaptation by T regs as well as expansion of other immunoregulatory cell populations such as NK cells, so that DAC can impact MS pathology without causing nonspecific immunodepletion. The proposed indication for DAC is treatment of patients with relapsing forms of multiple sclerosis (MS). The proposed dose is 150 mg injected subcutaneously once a month.

With respect to safety issues, Dr. Villalba notes that T regs are critical to maintaining immunological tolerance against self-antigens and that T reg deficiency can lead to development of autoimmune disease. Dr. Villalba describes "Immune Polyendocrinopathy X-linked syndrome" (IPEX) characterized by eczema, inflammatory bowel disease, autoimmune endocrinopathy, and other autoimmune diseases and notes that several conditions cause "IPEX-like" syndromes including CD25 or IL2 receptor alpha (IL2 RA) deficiency.

DAC HYP is not approved for any other indication in the United States. A different formulation (Daclizumab Nutley) was marketed as Zenapax for prevention of transplant rejection but has been withdrawn due to limited usage.

- *Therapeutic context*

MS is a chronic, autoimmune and neurodegenerative disorder of the central nervous system that affects an estimated 2.5 million individuals worldwide. Dr. Villalba notes that twelve products are approved for use in patients with relapsing forms of multiple sclerosis in the United States. The available products have a variety of safety issues. Please refer to Dr. Villalba's review for a summary of important safety issues for the approved products.

- *Regulatory background and marketing history*

With respect to drug safety in humans, an increased incidence of transaminase elevations was observed in subjects treated with DAC compared to placebo in clinical studies, and 1 patient died of liver failure due to autoimmune hepatitis approximately 3 months after her last dose.

Protocols were amended to include LFT monitoring every 4 weeks throughout the studies (instead of just in the initial months of the study) and evaluation prior to the next dose, to provide guidelines for treatment interruption or discontinuation, and to limit concomitant treatment with hepatotoxic drugs, and an external independent Hepatic Adjudication Committee (HAC) was convened to evaluate specific hepatic events.

At an End of Phase 2 Study on September 25, 2008, it was noted that a QTc study would not be necessary if analysis from clinical trials did not suggest an effect on QT. A Pre-BLA meeting was held on October 8, 2014, for which specific safety information was agreed upon but was missing from the original application that was submitted on February 27, 2015. The information was submitted on April 2, 2015. The application was filed, and the 74-day Filing letter included several requests for information and clarification related to safety. As Dr. Villalba notes, among the multiple responses to requests for information, the April 2, 2015, submission was considered to be a Major Amendment.

There is no foreign marketing experience with DAC HYP. The Sponsor submitted a Marketing Authorization Application to the European Medicines Agency in 2015.

3. Product Quality

Please refer to the CMC review.

4. Nonclinical Pharmacology/Toxicology

Please refer to the nonclinical reviews. In the DAC development program, adverse effects of concern included skin lesions. In addition microglial aggregates were observed in brain and spinal cord, the significance of which in humans is unknown according to the sponsor.

5. Clinical Pharmacology

Please refer to the Clinical Pharmacology review. The following information is from Dr. Villalba's summary of information provided by the applicant and reflects the findings most relevant to safety.

Pharmacokinetics

- T_{max} is 1 week.
- Elimination half-life is 21 days; steady state is reached in 16 weeks at the proposed dose/schedule.
- The mean steady state trough concentration (~15 ug/ml) exceeded the 5.0 ug/ml concentration required to maintain full saturation of CD25 receptors.

Pharmacodynamics

- Saturation of CD25 receptors on T cells occurred within 8 hours of the first dose and was sustained throughout the monthly dosing interval.

- Expansion of NK cells occurred as early as 2 weeks after treatment initiation, continued to expand during the first 12-18 months of treatment (most of the increase during the first 6 months), and in the 2nd year approached a plateau that was sustained for at least 3 years of treatment.
- Tregs decreased within the first week of treatment initiation; nadir reached by approximately Week 8 and sustained for at least 3 years of treatment.
- After discontinuation of treatment, NK cells and Tregs returned to pretreatment levels within 20-24 weeks of the last dose and unoccupied CD25 receptor levels returned to baseline values by 24 weeks after the last dose.

6. Clinical Microbiology

Please refer to reviews by Drs. Bo Chi and Colleen Thomas.

7. Clinical/Statistical- Efficacy

Please refer to Dr. Larry Rodichok's review of efficacy.

8. Safety

8.1 Safety Review Approach

Dr. Villalba's review used the following pools in the analysis of DAC clinical safety:

Study 201 (1 year; DAC 150, DAC 300, or placebo q 4 weeks)

Study 301 (up to 3 years, DAC 150 q 4 weeks subcutaneously vs Interferon beta-1a 30 ug once weekly IM)

Total DAC HYP experience:

201 (and its 1 year extension 202)

301 (and its extension of up to 6.5 years, 203*)

303* (up to 3 years; extension to 301)

302* (a Phase 3 open label study with extension; up to 3 years)

* DAC 150; ongoing at the time of original BLA submission.

Supportive safety data include studies with daclizumab Penzberg (for MS) and daclizumab Nutley (for psoriasis, asthma, uveitis, ulcerative colitis), as well as postmarketing data from Zenapax and basilxumab (another anti-CD25 monoclonal antibody approved for prevention of acute renal transplant rejection).

In Study 201, study drug was administered by either the treating neurologist or the treating nurse. Confirmed relapses could be treated with intravenous methylprednisolone (IV MP) 1000 mg/day for 3-5 days, and concomitant IFN-B was allowed starting at Month 6 for confirmed relapse. Subjects who withdrew from the study were no longer followed except in the case of SAE or pregnancy.

In Study 301, DAC was administered in the clinic. Suspected MS relapses could be treated with IV MP; concomitant IFN-B was not allowed. According to the protocol, subjects who withdrew and had SAEs were followed by the Investigator until the event resolved, stabilized,

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or returned to baseline.

8.2 Review of the Safety Database

Adequacy of the drug exposure experience (i.e., the safety database)

A total of 2236 patients (5214 patient years) were exposed to DAC in the development program as of the Safety Update (SUR). The table below, from Dr. Villalba's review, shows duration of exposure at the proposed dose of 150 mg or higher. The exposure exceeds ICH guidelines of 1500 patients total, 300-600 patients for 6 months, and 100 patients for 1 year.

DAC Duration of Exposure

Number of patients with MS exposed to DAC HYP 150 mg or higher:			
Any exposure	>=12 months	>=24 months	>= 36 months or longer
N= 2236	N= 1576	N= 1259	N= 888

*SOURCE: Original ISS and SUR (6/25/15). SUR data includes 395 exposed for 4 years and 211 exposed for 5 years. At the time of the original submission the total DAC experience (n=1785) included only 146 patients from study 303.

The total number exposed to DAC 150 mg was 1943 and the number exposed to DAC 300mg was 293. However, Dr. Villalba notes that the calculation of exposure is based on assigned treatment, not actual treatment, and she notes that this number includes 21 patients from site 903 in study 201 in which the pharmacist purposefully administered active treatment to all patients (administering the wrong treatment) such that according to the study report all subjects allocated to placebo received DAC at an unknown dose at least once during the study and most received DAC 4 times or more. I agree with Dr. Villalba's decision that the type of adverse events in these patients could be consistent with either active drug or placebo, and that the intent to treat analysis appears acceptable for calculating the denominator.

In Study 201, mean time on study treatment was similar across treatment groups, approximately 320 days, and 81-87% of subjects received all planned doses (87% for placebo, 84% and 81% for DAC 150 and 300 mg, respectively). In Study 301, mean time on treatment was similar for the Interferon beta-1a group (approximately 100 weeks) and for the DAC group (approximately 102) weeks; subject years on treatment were similar for both groups – approximately 1777 subject years for Interferon beta-1a and 1797 subject years for DAC. Eighty percent of subjects in the Interferon beta-1a group and 84% in the DAC group remained in the study for at least 96 weeks.

As Dr. Villalba shows, treatment groups were well balanced with respect to age (mean age approximately 36 years across groups), gender (63-68% female), and weight and were similar to clinical trials with other MS products. There were only 49 patients in the 18-19 y.o. age group and only 2 patients older than 55 years. Across treatment groups and studies at least 90% of subjects were White. Study 201 included only non-US patients and Study 301 included 13% US and Canadian patients. The highest recruitment was from combined Eastern Europe, Mexico, Argentina, India, and Brazil.

Of note, Studies 201 and 301 excluded patients with a history of taking various immunosuppressant drugs for specific periods ranging from three months prior to the study to within a year of participating in the study. These limitations should be considered if the drug is approved.

8.3 Adequacy of Applicant's Clinical Safety Assessments

Because of the long half-life of DAC, analyses of AEs included events with an onset date up to 180 days after study drug discontinuation and I agree with Dr. Villalba that this is appropriate.

I agree with Dr. Villalba that the safety assessment methods were generally adequate. However, as she notes, glucose and calcium measurements (as well as uric acid and phosphorous) were not included as routine evaluation in clinical trials. Dr. Villalba notes that the Zenapax label carried a precautionary statement regarding hyperglycemia and increasing fasting glucose levels, and she notes that in the present application 22 patients had AEs consistent with diabetes. She also notes that the lack of calcium levels hampers evaluation of patients with AEs of fractures, lithiasis, and sarcoidosis. I note that the Zenapax label, last approved in 2005, listed hyperglycemia as an undesirable effect; "A total of 16% (10 of 64 patients) of placebo-treated patient and 32% (28 of 88 patients) of patients treated with ZENAPAX had high fasting blood glucose values. Most of these high values occurred either on the first day post-transplant when patients received high doses of corticosteroids or in patients with diabetes."

As noted by Dr. Villalba, subsequent to a case of fatal autoimmune hepatitis in Study 202, protocol amendments to Study 302 increased monitoring for laboratory signals related to hepatic function and updated criteria for temporary suspension or discontinuation of study treatment for elevations in ALT, AST, or total bilirubin. The list of prohibited medications also increased with respect to risk of hepatotoxicity. Protocol amendments also gave additional guidance on evaluation and management of cutaneous and hematologic events and depression.

As previously mentioned, a pharmacist purposely dosed all 21 subjects from site 903 in study 201 with DAC instead of the assigned treatment and these subjects were not excluded from the safety analysis. Dr. Villalba notes that the types of adverse events these patients presented could be consistent with active drug or placebo (except for 1 case of diabetes insipidus), and I agree with her that the intent to treat analysis appears acceptable.

I agree with Dr. Villalba that the presentation of data for safety analyses in the application is of poor quality. Please see her review, Section 8.3.1, for details. Dr. Villalba notes extensive splitting of AE terms. Deficiencies in the adverse event (AE) datasets at the time of filing were not adequately corrected and remained of poor quality when updated datasets were submitted.

As Dr. Villalba notes, inadequacies in follow-up of patient outcomes, miscategorizations of AEs as non-serious when in fact they were serious, and failure to adequately capture all relevant events in the datasets may lead to under-representation of the extent of toxicity and impair characterization of incidence, duration, and reversibility for AEs found in this submission. Dr. Villalba has identified some serious AEs, by reading the narrative, that were

not captured in the datasets. The database did not adequately capture withdrawals as some were only listed as interruptions. Dr. Villalba notes that sometimes the database listed outcomes as no action taken with drug when the drug had already been discontinued because it had been the last dose in the study. She gives an example of 90 subjects with events leading to drug interruption in the hepatobiliary and Investigations SOCs for whom 14% discontinued due to an AE close to that date, but were not included in numbers of subjects with AEs leading to withdrawal. I believe that labeling can describe the range and degree of toxicity. Although the outcome information is not available for many cases, I believe labeling can describe the uncertainty.

8.4 Safety Results

Dr. Villalba has identified a number of important safety concerns that occurred in the clinical trials for daclizumab. These issues occurred to a greater extent in subjects receiving DAC than either placebo (in Study 201) or Interferon beta-1a (in Study 301). In several cases, Dr. Villalba shows that the rates of the events continue to increase over several years of therapy. Safety events identified as SAEs in the controlled trials are consistent with AEs resulting in discontinuations and with those identified as TEAEs (serious and nonserious). Throughout my review (and that of Dr. Villalba) the adverse events exclude events of MS or MS relapse. Overall, there was an imbalance in SAEs, Discontinuations, and TEAEs in the controlled trials for DAC compared to placebo in Study 201 or for DAC compared to Interferon beta-1a in Study 301, as shown in the table below.

Patients with SAEs, Discontinuations, or TEAEs (each excluding MS or MS relapse)

	Study 201			Study 301		Total DAC n=2236
	Placebo n=204	DAC 150 n=207	DAC 300 n=208	Interferon beta-1a n=922	DAC n=919	
All SAEs (excluding MS relapse)	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%

Dr. Villalba notes that AE dropouts occurred throughout the study periods; in Study 301 dropouts separated from Interferon beta-1a after about 500 days.

Dr. Villalba identified no adverse events of aplastic anemia in the clinical development program. She did identify events of acute pancreatitis and events that she considers to be drug reaction with eosinophilia and systemic symptoms (DRESS), although I do not believe these clearly meet the definition of DRESS. One case (203-901-006) was reported as Stevens Johnson Syndrome (SJS), although the expert dermatologist report did not believe it was SJS and there were no other cases of SJS or toxic epidermal necrolysis (TEN). Dr. Villalba identified an event of pancytopenia in a narrative (not included in the datasets) in subject 303/453-048 with brucellosis¹. There was one event of agranulocytosis (301/660-007) that Dr.

¹The incidence of pancytopenia with brucellosis reportedly ranges from 3-21% (Sari I, Altuntas F, Hacioglu S, et

Villalba believes may have been related to treatment with sulfa drugs and unlikely related to DAC.

Safety issues of concern in Dr. Villalba's review include:

- Drug-induced liver injury (DILI) that includes 1 death, 1 liver failure, and many cases of DILI
- Immune/Autoimmune-Mediated Reactions (in addition to those captured under 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 multiorgan failure; and lymphadenopathy.
- Skin Reactions
- Acute Hypersensitivity, including anaphylaxis and angioedema
- 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

I first discuss deaths in the database. Next I discuss safety issues of concern that I have identified above and then other serious adverse events, incorporating information from SAEs, Discontinuations, TEAEs, and labs, as appropriate. That is followed by a summary of TEAEs. I finish Section 8.4 with a summary of the other issues discussed in Dr. Villalba's safety review (including laboratory values, vital signs and electrocardiograms and immunogenicity).

Deaths

Five deaths (5/2336, 0.2%) occurred in the DAC clinical development program overall; 4 on DAC 150, 1 on DAC 300 vs none on placebo and 5 on Interferon beta-1a. The five deaths in DAC-treated subjects were: 1 of autoimmune hepatitis, 1 of complications subsequent to a severe cutaneous reaction, both likely related to DAC use; 2 of complications subsequent to aspiration pneumonia in patients with advanced MS, for which a role for DAC in increasing the risk of infection cannot be ruled out; and 1 of subdural and subarachnoid hemorrhage after a fall. Please refer to Dr. Villalba's review for details; I summarize the deaths below.

Subject 202/909-001 was a 45 y.o. female who died of consequences of *autoimmune hepatitis, liver failure, and multiorgan failure*. She had received 1 year (13 doses) of DAC 300mg in study 201. In Study 202 she received 4 doses of placebo (with 6 months off of DAC), followed by 3 doses of DAC 300 mg. On the day of the 2nd dose of DAC in Study 202, ALT was > 5X ULN and ALT was 4X ULN and on the date of the 4th dose, ALT and AST were

al. Am. J. Hematol. 83:334–339, 2008).

12X ULN, and bilirubin and alk phos were slightly elevated. The maximum ALT was 18X ULN, AST 33X ULN, and bilirubin 20X ULN. Please refer to Dr. Villalba's review for details of this case and please refer to a discussion of hepatotoxicity in Submission Specific Safety Concerns, section 8.5.1 of her review and on p. 16 of my review. Of note, this subject received tizanidine, a hepatotoxic drug, approximately 1 month prior to the transaminase increases; duration of exposure to tizanidine is not noted in the narrative but according to the information provided by the sponsor, she was taking no concomitant therapy at the time of ALT elevation. The Hepatic Adjudication Committee considered this case autoimmune hepatitis related to DAC. Subsequent to this case protocols were amended to include more rigorous monitoring and evaluation before each dose and to exclude patients with drugs that might confound assessment of liver toxicity.

Subject 201/304-006, with a history of rash with penicillin and trimethoprim presented with elevated ALT on Day 169 in Study 201 and discontinued on Day 308 (last treatment on that day, 12th dose) because of ALT/AST increase up to 3X ULN and mild increase in ALP. Liver enzymes improved after drug discontinuation. She had mild forehead rash with first dose of DAC that resolved without treatment. On Day 326 (2.5 weeks after last dose of DAC) she developed a *severe cutaneous drug reaction* (extensive maculopapular rash on feet, hands, chest, abdomen, and back; desquamative; with mucosal involvement) leading to *hospitalization and complicated with bacteremia, bilateral retinal vein thrombosis, psoas abscess, and ischemic colitis*, treated with anticoagulants complicated with GI bleeding requiring resuscitation. Antidrug antibodies were present since Day 169 (supportive of a drug allergy). Based on the autopsy the ultimate cause of death was psoas abscess causing ischemic colitis, but I agree with Dr. Villalba that it likely was in some part a consequence of an infectious complication of the severe cutaneous reaction. The skin biopsy was consistent with a drug reaction of the "lichenoid type" and I note that lichenoid skin reactions can occur weeks to months after exposure to the suspect medication² as in this case. I note that erythema multiforme and toxic epidermal necrolysis (TEN) are types of lichenoid dermatoses, but as Dr. Villalba notes there is not enough information to determine whether this case was SJS/TEN or even a case of DRESS (because of liver involvement).

Subject 301/431-004 died of septic shock and multiorgan failure subsequent to *aspiration pneumonia following MS relapse* that occurred 2 months after the last dose of DAC (discontinued because of cutaneous reaction). Subject 301/744-007 died from complications of *MS relapse and aspiration pneumonia* (eventually complicated by sepsis) that began after 4 doses of DAC. Although neither of these deaths appear directly related to DAC, I agree that the immunosuppression from DAC (and from azathioprine that was given for MS relapse in the second case) could have contributed to the serious infections.

Subject 303/537-012 died of *subdural and subarachnoid hemorrhage after a fall* (after treatment with heparin because of venous thrombosis for which, as noted by Dr. Villalba, patients with MS have an increased risk³). This death does not appear directly related to DAC.

² http://www.medscape.com/viewarticle/744497_15

³ Peeters PJHL, Bazelier MT, Uitdehaag BMJ, Leufkens HGM, De Bruin ML, de Vries F. The risk of venous thromboembolism in patients with multiple sclerosis: the Clinical Practice Research Datalink. *J Thromb Haemost* 2014;12: 444–51

Interferon beta-1a deaths were acute myocardial infarction in a patient with a cardiac history, peritonitis after laparotomy, suicide 1 month after last dose of Interferon beta-1a, pancreatic cancer, progression of MS 6 months after stopping Interferon beta-1a. I agree they do not appear related to Interferon beta-1a.

In summary, 2 of the 5 deaths that occurred in patients treated with DAC appear related to study drug (one autoimmune hepatitis and one infectious complication of a serious cutaneous reaction) and 2 others involved serious infection for which a role for DAC cannot be ruled out.

Submission Specific Safety Issues

Drug-Induced Liver Injury (DILI)

DAC is associated with DILI. There was one death due to DILI, discussed above. SAEs and discontinuations in the *Hepatobiliary disorders* or listed under *liver investigations HLTG in the Investigations* SOC occurred more frequently in DAC than in control in the controlled trials. Transaminase elevations for DAC were greater than for control in the controlled trials. TEAEs of ALT or AST increased were greater for DAC than for control and were among the most common ($\geq 5\%$) TEAEs in the controlled trials. At least 4 Hy's law cases were identified in the clinical trial database for which a role for DAC cannot be ruled out. At least 7 cases of DILI (2 of the Hy's law cases including the death) were autoimmune hepatitis. I agree with Dr. Villalba that the findings regarding DAC-induced DILI are concerning. Onset of DILI is unpredictable, it occurs despite monitoring, it can be fatal, and risk factors to predict patients who are susceptible are not yet identified. I recommend a Boxed Warning for DILI and recommendations for stringent monitoring. As suggested by Drs. Villalba and Avigan, even monitoring will not fully eliminate risk for a life-threatening hepatotoxic event.

SAEs and Discontinuations in the *Hepatobiliary disorders* or listed under *liver investigations HLTG in the Investigations Soc* and Transaminase Elevations

	Study 201			Study 301		Total DAC
	Placebo n=204	DAC 150 n=207	DAC 300 n=208	Interferon beta-1a n=922	DAC n=919	n=2236
SAEs in	0.5%	1.4%	0.5%	0.8%	0.9%	1.3%

Hepatobiliary Disorders and Investigations (Hepatobiliary HLGT)						
SAEs related to DILI	0.5%	1.0%	0.5%	0.1%	0.5%	0.9% ^a
Discontinuations	0.5%	1.4%	0.5%	3.9%	5.3%	6.4%
TEAEs (at least 5%) in Investigations SOC						
ALT increased	2%	5%	6%	7%	8%	8%
AST increased				5%	5%	6%
Outlier Analysis of ALT^b						
ALT > 3X ULN	3.4%	7.7%	6.7%	8.2%	9.5%	9%
ALT > 5X ULN	1%	4.3%	3.8%	3.2%	5.8%	6%
ALT > 10X ULN	0	3.4%	1.4%	1.2%	2.6%	3%
ALT > 20X ULN	0	1.4%	1.0%	0.4%	0.9%	<1%
ALT > 3X ULN, BR > 2X ULN, ALP < 2X ULN	0.5%	0.5%	0.5%	0.1%	0.7%	0.8%

Information in the table is extracted from Dr. Villalba’s review, except TEAEs for Total DAC that are from the SUR.

^a Includes 20 SAEs of DILI; 21 cases would also be 0.9%.

^bDr. Villalba notes that more patients had BR > 2 X ULN with no increase in ALT or AST on DAC (24 subjects, 2.6%) vs Interferon beta-1a (4 subjects, 0.4%) in Study 301 that could be consistent with Gilbert’s or given the imbalance perhaps an obstructive component of DAC induced hepatotoxicity.

Dr. Villalba identifies 21 DILI SAEs in the Total DAC database (16 identified by the sponsor through the SUR, 3 additional after the SUR, and 201/509-007 (coded as arteriovenous malformation under Congenital instead of ALT inc under Hepatobiliary or Investigations) as well as a case of cholangitis that she believes is DILI but Dr. Avigan believes is bacterial.⁴ Please refer to Section 13.3.4.1 of her review for a list of subjects with DILI and to SAEs, Laboratory Findings and Section 8.5.1 of her review for a discussion of the issue.

All SAEs in the Hepatobiliary SOC led to drug withdrawal. Dr. Villalba notes that the majority of withdrawals in the Investigations SOC were non serious, and that patients with ALT or AST > 5X ULN had to be withdrawn with procedures put in place after the fatal hepatotoxic event. She notes that many of the non-SAE that led to drug withdrawal in hepatobiliary and investigations SOCS were confounded by use of other potentially hepatotoxic medications or possible infections and some occurred in patients who had also developed some kind of rash, lymphadenopathy, and in 1 case Crohn’s disease. She also notes among the discontinuations a case consistent with Primary Biliary Cirrhosis (PBC) in a 51 y.o. female on Day 113 of DAC (302/622-108) who she proposes may have had underlying PBC exacerbated by DAC use.

Time to onset for SAEs of DILI ranged from 57 days to more than 3 years of exposure to DAC, and some events started up to 2 months after the last dose of DAC. The events included

⁴ Dr. Villalba also believes that a case of brucellosis and a case of yersiniosis are DAC-related DILI, as well as a case with ALT > 30X ULN coded as “celiac disease causing elevated liver enzymes”.

increases in ALT up to 67X ULN, AST up to 48X ULN, and BR up to 7X ULN. Some had concomitant other immune-mediated adverse reactions, such as cutaneous reactions. Many cases were confounded by viral infections or by hepatotoxic medications⁵, although Dr. Villalba notes that the use of potentially hepatotoxic medications was balanced in Study 301. Although it is not possible to attribute definitively the cases to DAC, there is an imbalance in the controlled trials, and I agree with Dr. Villalba that DAC most likely played a role in these cases and that DILI is an important safety concern with DAC.

Dr. Villalba notes that at least 8 patients received high dose corticosteroids, including 3 also treated with azathioprine, for suspected autoimmune hepatitis (AIH). All DILI SAEs but the fatal event resolved one to several months after DAC discontinuation, with or without corticosteroid treatment (although some are still on low dose corticosteroids (one of them >2.5 years later) and I agree with Dr. Villalba that these should not be considered resolved.

An exploratory genome-wide association study (GWAS) conducted by the Sponsor did not identify a genotype that could predict DAC-associated liver disease in individual patients. Other risk factors have not been identified, although Dr. Avigan suggests that individuals predisposed to autoimmune disease may be at risk for AIH.

Dr. Villalba shows that the risk for SAEs in this SOC increased after 200 days on DAC. The cumulative rates of all AEs in this SOC similarly increases over time up to about 300 days in Study 201 and up to about 800 days in Study 301 before beginning to plateau. In Study 301, the cumulative rate of events separates from Interferon beta-1a beyond approximately 200 days.

Drs. Avigan and Villalba have identified at least 7 cases of AIH (7/2236, 0.3%) probably or possibly related to DAC.⁶ Dr. Villalba calculates a rate of AIH in the database of at least 7/5214 PYRs or 134 per 100,000 patient years (PYRs). She compares this to the overall incidence in the general population of 2 per 100,000 per year (of which an estimated 9% are drug-induced), or as cited in another publication, 23.8 per 100,000 PYRs in untreated MS patients. Dr. Avigan notes that in contrast to idiopathic AIH, many of the DAC DILI cases were not associated with high titers of serum antinuclear antibodies (ANA) or other autoantibodies. Dr. Avigan notes that in a few cases there were substantial titers of these antibodies, suggesting that DAC may also “exacerbate or unmask underlying autoimmune diatheses involving the liver”. Of note, subject 303-649-009 had a positive ANA titer, previously had autoimmune thyroiditis on interferon beta-1a in Study 301, and developed thrombocytopenia after discontinuation of DAC following tapering of steroids that had been used to treat AIH. Subject 301/205-006 had a history of hypothyroidism before starting DAC, and after development of AIH was noted to have positive ANA titers characteristic of AIH, and Dr. Avigan suggests that the subject could have had underlying AIH aggravated by

⁵ Confounding medications included escitalopram, metamizole, pulse methylprednisolone, carbamazepine, valproic acid, acetaminophen, gabapentin, tizanidine, lamotrigine, propylthiouracil, and amoxicillin.

⁶ Subjects 202/909-001, 203/506-011, 203/508-012, 301/670-035, 302-622-103, 303-649-009, and 301-205-006. Dr. Avigan believes that elevated transaminases in subject 202-765-003 reflected alterations induced by Gilbert’s Syndrome (mildly elevated bilirubin) and thyrotoxicosis (elevations in ALP and ALT), rather than DAC, but wondered whether DAC unmasks or aggravates thyroid autoimmune conditions.

DAC. According to the NIH Livertox website (http://livertox.nih.gov/Phenotypes_auto.html), the most important element in management of drug-induced AIH is to recognize the possible role of the medication and discontinue it promptly; it recommends that high dose corticosteroid therapy is appropriate if recovery does not start within 1-2 weeks of discontinuing the drug or if there is any evidence of hepatic failure, and that follow-up should take place for at least 6 months after steroid discontinuation to document full recovery and absence of relapse.

Hy's Law refers to the recognition that hepatocellular injury sufficient to impair bilirubin excretion is an "ominous indicator of the potential for a drug to cause serious liver injury"⁷. Dr. Villalba identified 17 subjects with biomarker values in the Hy's law range (ALT or AST $\geq 3X$ ULN, Total BR $\geq 2X$ ULN, ALP $< 2X$ ULN). As Dr. Villalba notes, most of the cases were confounded (or may have had an obstructive component). However, there are 4 Hy's law cases for which I agree a role for DAC cannot be ruled out (although 2 may be confounded):

Subject 201/454-019. This subject started hydroxyzine and escitalopram approximately 30 days prior to the event, and the indication listed for both was depression. Event started 1 month after last dose of DAC and resolved 2 months later without use of corticosteroids. Escitalopram labeling includes fulminant hepatitis, hepatic failure, hepatic necrosis, and hepatitis in postmarketing experience) It is not clear from the narrative or the patient profile that escitalopram was discontinued.

Subject 202/909-001. Fatal hepatic failure after restarting DAC after 6 month washout. Not obviously confounded. (*Autoimmune hepatitis*)

Subject 301/624-012. Life-threatening acute hepatic failure with jaundice, hypoalbuminemia, increased INR. Concomitant valproic acid and Herbalife. Dr. Avigan believes that the biopsy findings and elevated serum GGT levels are not characteristic of valproic acid induced liver toxicity, and he notes that the time frame and levels of exposure to Herbalife were not well documented.

Subject 303/649-009. *Autoimmune hepatitis*. In Study 301 received Interferon beta-1a and developed autoimmune thyroiditis, but liver enzymes were normal in that study. May have been pre-disposed to autoimmune disease.

The DILI Guidance uses the following major indicators of potential for severe DILI: excess of aminotransferase elevations to more than 3X ULN compared to control, marked elevations of aminotransferases of 5X, 10X, or 20X ULN in modest numbers of subjects in the test group and not seen (or seen much less frequently) in control, and one or more Hy's law cases.

According to the DILI Guidance, only the most overt hepatotoxins are expected to show severe DILI in a clinical trial database of the size in this BLA. 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 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). The DILI Guidance provides several examples of drugs (Troglitazone

⁷ Guidance for Industry. Drug-Induced Liver Injury: Premarketing Clinical Evaluation. 2009. <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM174090.pdf>

for Type 2 diabetes that was withdrawn when other drugs with similar efficacy but no hepatotoxicity became available and the NSAID bromfenac) with rates of DILI in clinical trials similar to DAC that were subsequently withdrawn postmarketing because of acute liver failure despite recommendations regarding monitoring.

Dr. Villalba does not believe that the serious risks associated with DAC could be minimized by adequate labeling and postmarketing measures including labeling and a REMS and believes it would be difficult to comply with the stringent eligibility, monthly monitoring, and stopping criteria used in clinical trials. She also believes that monitoring will not work, because serious toxicity did occur despite strict monitoring and stopping criteria and because the risk of DILI will be higher in a wider population using potentially hepatotoxic drugs that were excluded from the clinical trials. Dr. Senior shares these concerns about hepatotoxicity and the ability to mitigate the risk through monitoring and labeling and does not recommend approval. Dr. Avigan states that because underlying idiopathic AIH or other pre-existing autoimmune diatheses involving the liver may be exacerbated or unmasked by DAC HYP, the use of this agent in patients with these conditions should be contraindicated (or not recommended).

I believe that the degree of success in mitigating the risk of serious hepatotoxicity even with stringent patient selection and monitoring is an uncertainty. In the clinical trials, liver related fatality did not occur subsequent to implementation of such measures, although serious drug-related liver injury continued to occur. Patients with liver injury underwent biopsies and some required long-term treatment with high dose corticosteroids or azathioprine. Based on the results in the clinical trials, serious hepatotoxicity would certainly occur in the postmarketing setting. If DAC were approved, labeling would require a boxed warning for hepatotoxicity and details of the stringent monitoring would be required. A REMS would support the labeling. The uncertainties of time to onset, duration of treatment required in cases of hepatotoxicity, outcome even after treatment of hepatotoxicity, and other uncertainties regarding characterization of the hepatotoxicity would have to be stated. The Sponsor is proposing to have patients self-administer DAC. (b) (4)

At the time of this review, details of a REMS are being developed. Ideally, a biomarker (phenotype or genotype) predicting patients at risk would be found.

Malignancies

SAEs of malignancies (in the *Neoplasms* SOC) were generally balanced across drug and control in studies 201 and 301 with single instances of non-benign malignancies with the exception of melanoma that occurred in 2 subjects on DAC 300 in Study 201 but not elsewhere in the database. Breast cancer occurred in the extension studies at rates greater than that in the background population, as discussed below. Although the Sponsor's consulting hematopathologist/hematologist oncologist experts only assessed 1 case of lymphoma as probable, 3 subjects in the extension studies were treated for non-Hodgkin lymphoma (NHL); the rate of NHL (either for 1 or 3 subjects) in the DAC database is greater than background for patients < 65 y.o.. Without a comparator for the cases in the Total DAC database, it is difficult to characterize

the risk from DAC. Given the breast cancer in a male, a possibly increased rate in females, and a rate of NHL greater than background, I suggest monitoring cancer risk in a post-marketing study if DAC is approved. I would consider including these malignancies in the labeling.

	Study 201			Study 301		Total DAC
	Placebo n=204	DAC 150 n=207	DAC 300 n=208	Interfero n beta- 1a n=922	DAC n=919	n=2236
SAEs reported thru the SUR (benign and non-benign)	0.5%	0.5%	1.0%	1.2%	1.5%	1.3% ^a
Non-benign SAEs thru the SUR (in study 301 listed for DAC only)	Cervical carcinoma	Cervical carcinoma	Melanoma (2)		Uterine (1) Thyroid (1) Brain (1; day 24) Meningioma (1) Transitional cell carcinoma (1) Breast (1)	Breast cancer (5 females) ^b ; 10 other non-benign; ^a 15 benign
TEAEs	1%	1%	3%	4%	5%	5%

^a 30 total SAEs in the SUR; 15 non-benign including pulmonary carcinoid, ovarian, 1 anal carcinoma, as well as 4 breast cancer, in addition to those listed in Studies 201 and 301. Benign neoplasms were generally heterogeneous, although I note 3 uterine leiomyomas in study 301 and 1 in study 303, after 100 to 989 days of therapy, 1 resulting in discontinuation of DAC.

^b After the cutoff of the SUR, there were 3 additional cases reported in females (total of 8 cases) and 1 in a male; discussed below.

The most frequent malignancies in Total DAC were breast cancer in females, one occurring in controlled study 301. As of an update from the Sponsor on February 8, 2016, (after the cutoff of the SUR), there were 8 females diagnosed with breast cancer. Their ages were 36-52 y.o. and they were diagnosed 333 to 1980 days since starting DAC (1 occurred 1 year after stopping DAC although the patient had reactive lymph nodes that Dr. Villalba believes suggests the possibility of persistent DAC immunologic effects). The patients were from Germany, the Czech Republic, Poland, and Serbia, and none from the US. The rates of breast cancer in females in the total DAC population and in the background population are shown in the table below. This rate for DAC is higher than the SEER background rate in the US population for females of all ages of 126 per 100,000 (but the Sponsor notes that the SEER rate is within the 95% CI for DAC) and for females < 50 y.o. that may be the more relevant comparison because the mean and median ages of all subjects in the DAC database were 36 y.o. and there were no subjects > 56 y.o.. The rate for DAC is higher than in the background European population for all ages (but the Sponsor notes that the Globocan rate is within the 95% CI for DAC).

Females with	Rate of breast	SEER rate for	SEER rate	Rate of breast	European
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breast cancer in Total DAC	cancer in females in Total DAC	females of all ages ^b	for females < 50 y.o. ^b	cancer in European females in Total DAC ^a	background rate in females (Globocan)
8/1485 (0.5%)	185/100,000 PYRs [95% CI: 80.15 to 365.3] ^a (8/4311 PYRs)	126/100,000	43/100,000	212.4/100,000 PY [95% CI: 91.73 to 418.02]	119.5/100,000 PY (all ages) (note: in the age ranges of 40-55 y.o. the rates are 102.6 – 213 per 100,000)

^a Calculated by Sponsor in February 8, 2016, submission.

^b SEER 9 areas (San Francisco, Connecticut, Detroit, Hawaii, Iowa, New Mexico, Seattle, Utah, and Atlanta). Rates are age-adjusted to the 2000 US Std Population (19 age groups - Census P25-1130).

The Sponsor notes that all but one of the female subjects with breast cancer had 1 or more risk factors including family history, hormone replacement therapy, or smoking history, but I do not believe that this rules out a potential role for DAC. An increased risk is not biologically implausible given the immunosuppressive effects of DAC. According to the Sponsor, the literature suggests that the incidence rate of breast cancer among MS patients may be somewhere between 6% to 4 times greater than the rate observed in the general population. Identifying the most appropriate comparison is difficult, as is predicting the risk in the U.S. population. Without a comparator for the cases in the Total DAC database, it is difficult to characterize the risk of breast cancer in females exposed to DAC.

One case of breast cancer occurred in a male patient from the United States. He had at least 36 doses of DAC prior to the event. The incidence of male breast cancer in the DAC database as of December 21, 2015 is 0.1% (1/751) or 43 per 100,000 PYRs (1/2323 PYRs). This rate is greater than the SEER rate in the background population for males of all ages (1/100,000).

Lymphoma was not reported in the DAC database as of the SUR, although after the cut-off of the SUR there were 4 subjects diagnosed with non-Hodgkin lymphomas (NHL), all in patients treated with DAC for 1.5 to 7 years. In 1 subject NHL is regressing after discontinuing DAC, without treatment. Subject **203-500-003** (originally suspected to have peripheral T cell lymphoma; the Sponsor’s expert hematologist/oncologist concluded atypical T-cell population with follicular disruption without evidence of a Tcell lymphoma)⁸ had regression following discontinuation without specific treatment. Three of the subjects were treated with therapy for NHL, although the external hematopathologist and hematologist/oncologist consulting for Biogen Idec did not believe there was convincing evidence of lymphoma for 2 of the 3:

303/678-004 Dr. Villalba notes that the biopsy report favored “partial (~30-35%) lymphoganglionic infiltration of grade 3A follicular, B-cell non-Hodgkin's malignant lymphoma.” The patient was treated with RCHOP. However, the Sponsor’s expert

⁸ March 3, 2016 response to IR.

hematopathologist stated that “the current biopsy does not provide unequivocal evidence of a non-Hodgkin B or T-cell lymphoma.” The Sponsor’s expert hematologist/oncologist said that a B cell lymphoma is probable.

203/761-004 Considered by the treating physician to be follicular lymphoma. The patient is being treated with rituximab. However, the Sponsor’s expert hematopathologist considered this to be florid reactive follicular hyperplasia (B-cell hyperplasia) without evidence of lymphoma.

203/453-003 diagnosed with peripheral T-cell lymphoma and treated with cyclophosphamide, doxorubicin, vincristine, prednisone and etoposide (CHOEP) . However, Sponsor’s experts considered it most likely a drug-induced (T-cell) lymphoid proliferation but did not see convincing evidence of NHL (T-cell Lymphoma).

Dr. Villalba notes that the rate of NHL in the database, based on the 3 treated subjects in 5214 PYRs, is 58 per 100,000 patient years, greater than the background population rate for age < 65 from SEER of 9.3 per 100,000 population per year for the years 2008-2012 (http://seer.cancer.gov/csr/1975_2012/browse_csr.php?sectionSEL=19&pageSEL=sect_19_table.07.html). Although 2 patients may have been treated as if they had NHL, the consultants did not find evidence to support that diagnosis in these cases. Even 1 case in 5214 PYRs is 19.2/100,000 PYRs (the sponsor has calculated a rate of 15.9/100,000 PYRS), still higher than the SEER rate. The sponsor cites rates of lymphoma in the general population 19.6/100,000 [citing [National Cancer Institute 2014](#)] and 7.0/100,000 [citing [International Agency or Research on Cancer 2012](#)], but I believe that their cited rate from SEER/NCI reflects all ages (the rate for all ages cited on the SEER website is 19.7/100,000 and Globocan is 6/100,000). However, with a single case it is not possible to attribute this to an effect of DAC.

Skin and Subcutaneous Tissue Disorders

SAEs, discontinuations, and TEAEs in the *Skin and Subcutaneous Tissue Disorders* SOC occurred more frequently in DAC than in control in the controlled trials; overall, TEAEs in this SOC occurred in 40% of DAC-treated subjects. The events ranged from mild to severe and life-threatening reactions, some requiring treatment with systemic steroids, and some that required months to resolve after discontinuing DAC. I agree with Dr. Villalba that it would be difficult for a non-dermatologist to distinguish between many of the skin rashes and I agree with her that this is very important because the actions taken with the drug, the urgency of the situation, and the treatment required depend on the type of skin reaction. I agree with Dr. Villalba that an analysis of the rate of eczematous and psoriatic conditions among patients who had a prior history of such conditions vs those who did not might help identify patients at risk for such DAC-induced reactions. I would also recommend that the Sponsor evaluate whether there is a biomarker predictive of specific skin reactions.

SAEs, Discontinuations, TEAEs overall, and TEAEs ≥5% on DAC and > placebo in Study 201 or at least as frequent as Interferon beta-1a in Study 301 in the Skin and Subcutaneous Tissue Disorders SOC

	Study 201			Study 301		Total DAC
	Placebo	DAC 150 n=207	DAC 300 n=208	Interfero n beta-	DAC	

	n=204			1a n=922	n=919	n=223 6
SAEs	0%	1%	1.4%	0.1%	1.5%	2%
		Rash, Dermatitis exfoliative	Dermatitis allergic, Dermatitis atopic, Erythema nodosum	Dermal cyst	Angioedema (2), Leukocytoclastic vasculitis, DRESS, Psoriasis (2), Toxic skin eruption	
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 ^b	2%	3%	6%	6% ^c	14% ^c	14%

^a I combined rash, rash macular, and rash maculopapular from Table 35 of the report for Study 201 consistent with the Sponsor's grouping in the report for Study 301. TEAEs in Total DAC are from SUR.

^b I combined eczema, dermatitis, dermatitis allergic, dermatitis atopic, and seborrheic dermatitis, and dyshidrosis from Table 35 of the report for Study 201, consistent with the Sponsor's grouping in the report for Study 301. TEAEs from Total DAC are from the SUR.

^c The terms reported here are from Table 219 of the study report for Study 301 and combine multiple terms for Rashes, Eruptions, and Exanthems. Dr. Villalba provides the same findings from the JumpStart Team in Section 8.5.2 of her review.

Dr. Villalba shows that the risk for SAEs in this SOC increased after 200 days on DAC. The cumulative rates of all AEs in this SOC similarly increases over time up to about 300 days in Study 201 and up to about 800 days in Study 301 before beginning to plateau. In Study 301, the cumulative rate of events separates from Interferon beta-1a beyond approximately 200 days.

In addition to the SAEs noted above in Studies 201 and 301 and additional cases of those terms in the Total DAC Pool, SAEs in the Total DAC pool included hidradenitis, papulosquamous conditions, lichenoid keratosis, photodermatitis, urticaria, and erythema multiforme, as well as an event of cutaneous sarcoidosis, an event of parapsoriasis (a pre-malignant condition), and an event of cutaneous vasculitis. A subject may have had more than 1 event, such as subject 301-660-008 with cutaneous vasculitis in Study 301, treated with steroids who developed erythema multiforme in Study 303. An event of Stevens Johnson Syndrome (SJS) was reported (203/901-006), but not confirmed and was felt by the Sponsor's expert dermatologist not to be SJS.

In addition to the AEs noted above and additional cases of those in Total DAC, Dr. Villalba also notes AEs in this SOC that occurred in < 5% but with a ≥3% risk difference or ≥3x relative risk in DAC vs Interferon beta-1a including angioedemas, bullous conditions, dermal and epidermal conditions, exfoliative conditions, photosensitivity and photodermatoses, psoriatic conditions, and rosaceas.

Dr. Villalba notes that reactions ranged from mild reactions managed with topical treatment to life threatening reactions including complications likely contributing to 1 death. She notes that some of the rashes were associated with alopecia and scarring. She notes 6 cases of cutaneous vasculitis and 1 of panniculitis (inflammation of subcutaneous adipose tissue) that she notes require immediate drug discontinuation and starting of aggressive immunosuppressive treatment in some cases. Among the severe SAEs was **Subject 301/512-002** with toxic dermatitis who was barely able to walk due to vesicles on her feet.

Some AEs required hospitalization, or treatment with corticosteroid therapy or drugs such as topical cyclosporine. Dr. Villalba notes that at least 2 subjects had mild psoriasis at entry and had exacerbation of psoriasis requiring UV treatment. Some patients were treated with plasmapheresis with the goal of removing remaining drug, and resolved several months after drug discontinuation (e.g. 9 months in **Subject 301/512-002**). Four SAE were reported as not resolved at the time of the submission (including subject **301/152-004** with exfoliative dermatitis that had not resolved, despite treatment with prednisone, 11 months after DAC discontinuation). Please refer to Dr. Villalba's review for a complete list.

Dr. Villalba notes that the role of plasmapheresis in treating the skin reactions is unclear. At the "Late Cycle Meeting" on February 24, 2016, the Sponsor clarified that plasmapheresis had been carried out by one investigator and that its role in removal of DAC had not been evaluated. It would be useful to have information about whether plasmapheresis removes daclizumab and how long it takes to get to an undetectable level.

The Central Dermatologist, (b) (4) identified most cutaneous events as eczema or psoriatic events. Psoriatic conditions occurred in 2% of patients on DAC vs 0.3% on Interferon beta-1a in Study 301. Dr. Villalba notes that eczema and psoriasis are not uncommon in the general population and the rates in the DAC database were within the background in the general population. According to the Central Dermatologist Report (b) (4) found in the Summary of Clinical Safety, the background rate of psoriasis in adults of European ancestry is 3%. The report suggests that about 30% of adults may be susceptible to atopic dermatitis, a T-cell mediated inflammatory disease in which eczema is common. Still, there was an excess in DAC vs comparator and Dr. Villalba as well as the Central Dermatologist provide a detailed discussion of mechanisms that impart biologic plausibility to the serious dermatologic AEs (b) (4) concludes that "A reasonable plan for management of cutaneous adverse events post approval of this drug could be to inform prescribers what to expect, recommending referral to a dermatologist for further evaluation for clinically worrisome skin reactions."

Infections

SAEs in *Infections and Infestations* occurred more frequently in DAC than in control in the controlled trials. TEAEs in this SOC occurred slightly more frequently in DAC than in control. The *Infections* SOC accounted for the most SAEs in the Total DAC database, but resulted in few discontinuations. SAEs included bacterial, viral, and mycobacterial infections. In several cases, I agree with Dr. Villalba that immune-mediated reaction vs infection cannot be ruled out.

SAEs of Infections that occurred in at least 2 subjects on DAC in a given study in the controlled trials and more frequently than control are shown in the table below.

	Study 201			Study 301		Total DAC
	Placebo n=204	DAC 150 n=207	DAC 300 n=208	Interfero n beta- 1a n=922	DAC n=919	n=2236
SAEs of Infections Overall	0%	2.9%	1.5%	1.6%	4.4%	4.4%
Urinary Tract Infection ^a	0%	0.5%	0%	0.3%	1.2%	0.9%
Pneumonia/Lobar Pneumonia				0.2%	0.8%	0.7%
Appendicitis/Appendicitis perforated	0%	0.5%	0%	0%	0.3%	0.2%
Cellulitis	-	-	-	0%	0.2%	0.1%
Enteritis/Enterocolitis infectious	-	-	-	0%	0.2%	<0.1%
Viral Infection	0%	1.4%	0%	0.2%	0.8%	0.6%
Discontinuations	0%	0.5%	0.5%	0.3%	0.5%	0.8%
TEAEs	44%	50%	54%	57%	65%	59%

^aUrinary Tract Infection includes Cystitis/urinary tract infection, genitourinary tract infection, pyelonephritis/pyelonephritis acute, and urinary tract infection; does not include urosepsis.

Dr. Villalba notes that the most common serious infections with DAC overall were respiratory tract infections (at least 36 subjects (1.6%) in the total DAC database); these were driven by lower respiratory tract infections, primarily pneumonia, but also included 3 cases in an extension study consistent with atypical pneumonia or immune mediated pneumonitis. One SAE of pulmonary tuberculosis in Study 301 occurred in a DAC-treated subject. An SAE of “probable tuberculosis” occurred after the cutoff of the SUR (and which Dr. Villalba thinks may be consistent with sarcoidosis if no infection is found); that patient is being treated empirically with antifungals (for a differential diagnosis that includes aspergillus) and anti-TB drugs with follow-up pending at the time of review. Dr. Villalba notes 4 “non SAEs” of tuberculosis reported with DAC. I agree with Dr. Villalba’s recommendation (in the discussion of discontinuations) that if approved, patients should be screened for latent tuberculosis prior to receiving DAC.

Dr. Villalba notes other serious bacterial infections: one case each of hepatic yersiniosis (201/752-018), brucellosis with pneumonia and liver involvement (303/453-048) that she notes lacked data to support the diagnoses and proposes that they are consistent with a systemic inflammatory reaction to DAC. Similarly she notes 2 cases of clostridium difficile colitis (in studies 202 and 302) with no data to support the diagnosis and proposes that these are cases of non-infectious inflammatory colitis. She notes 1 case of neuroborreliosis and 2 cases of Lyme disease in patients on DAC in Study 301. Two cases of sepsis following aspiration pneumonia (described under deaths) are not directly attributable to DAC, and one SAE of urosepsis occurred in a patient on DAC that cannot clearly be attributed to DAC as Dr. Villalba notes urosepsis is a risk in MS; however, in neither case can a role for DAC be ruled out. There were 3 cases of multiorgan failure with associated sepsis and it is unknown if the multiorgan failure could be due to infection or immune-mediated.

As shown above, there was an excess of serious viral infections in studies 201 and 301. Dr. Villalba notes that the 13 cases in total DAC occurred after 9 to 76 doses of DAC and that

approximately half were considered severe. The *cases on DAC in the controlled trials* included 1 case each of CMV hepatitis (with positive IgG and IgM, consistent with reactivation) and chronic hepatitis B, varicella, Hepatitis A, influenza with upper respiratory tract infection, one viral meningitis (although this was not treated with antibiotics or antivirals and daclizumab was not discontinued), 1 dengue, and 3 not specified (vs viral myocarditis, chicken pox, and viral syndrome not otherwise specified for Interferon beta-1a). The *total DAC database* also include SAEs of infectious mononucleosis (although they were not IgM positive and Dr. Villalba proposes that they are cases of DILI), and facial herpes zoster. There was one case of aseptic meningitis (202/363-008) that Dr. Villalba believes could be consistent with immune mediated meningitis (noting that a case of aseptic meningitis in association with pneumonitis and hepatitis occurred with DAC Penzberg).

As shown in the table above, TEAEs in the Infections SOC occurred slightly more frequently for DAC than for placebo in Study 201 or for Interferon beta-1a in Study 301. The most common infections ($\geq 5\%$ in any DAC group and greater than placebo) in Study 201 were upper respiratory tract infection (URI)/URI viral, pharyngitis, oral herpes, influenza, and urinary tract infection. The most common infections ($\geq 5\%$ in any DAC group and at least as frequent as Interferon beta-1a) in Study 301 were nasopharyngitis, URI, influenza, pharyngitis, bronchitis, and oral herpes. The most common TEAEs for Total DAC reflected those in Studies 201 and 301.

Dr. Villalba shows that the risk of SAEs of infections increased vs comparator over time, and in Study 301 separated from Interferon beta-1a beginning at Day 200.

Gastrointestinal Disorders (Immune-Mediated)

SAEs, discontinuations, and TEAEs in the *Gastrointestinal Disorders* SOC occurred slightly more frequently in DAC than in control in the controlled trials, particularly for colitis-related events as shown in the table below. I discuss colitis-related events and other immune-related gastrointestinal events in more detail following the table.

SAEs, Discontinuations, TEAEs overall in the Gastrointestinal Disorders SOC

	Study 201			Study 301		Total DAC
	Placebo n=204	DAC 150 n=207	DAC 300 n=208	Interferon beta-1a n=922	DAC n=919	
SAEs	0.5%	1.4%	1.0%	0.7%	1.2%	1.6%
SAEs of Colitis-Related Events	0%	0%	0.5% ^a	0%	0.3% ^b	0.5% ^c
Discontinuations	0%	0%	0%	0.1%	0.3%	0.8% ^d
TEAEs	11%	16%	14%	23%	30%	25%
TEAEs of Colitis-related events				0%	1.4%	1.2%

^a 1 case of Crohn's disease

^b 1 ulcerative colitis, one colitis, and one enterocolitis

^c 12 cases of colitis consistent with inflammatory colitis (colitis, colitis ischaemic, colitis microscopic, colitis ulcerative, enterocolitis/enterocolitis haemorrhagic)

^d 21 events in 19 subjects; includes 1 each of lip swelling, mouth edema, and oral pain

The SAEs are notable for several colitis-related events on DAC that did not occur in placebo or Interferon beta-1a in the controlled studies. Overall, 27 subjects in the total DAC pool had AE of colitis. Dr. Villalba suggests that 2 SAEs of C difficile colitis, discussed under the Infections SOC, are non-infectious inflammatory colitis. The cases of colitis occurred after 7 to 50 doses of DAC. Dr. Villalba notes that sometimes a specific diagnosis was made a few weeks or months after initiation of symptoms that included bloody diarrhea. Treatment of colitis included standard therapy for these conditions including sulfasalazine, mesalazine, antibiotics, budesonide, as well as IV or oral corticosteroids and azathioprine. She notes that some patients required hospitalization with blood transfusions and electrolyte replacement for severe dehydration and bleeding.

Dr. Villalba notes that 11 of the 27 subjects with colitis discontinued drug treatment. She notes that as of the SUR, 14 events had not resolved, including 4 that led to drug withdrawal. Subject 303/611-012 with ulcerative colitis required 6 months after discontinuation for resolution (with sequelae) and subject 203/404-011 had colitis that was stable but ongoing 3 years after the last dose of DAC. Dr. Villalba notes that even for “resolved” cases it is unclear if the patient still required treatment for inflammatory bowel disease. I agree with Dr. Villalba that an event should not be considered resolved if an event still required treatment. She notes that the resulting hospitalizations, invasive procedures such as duodenoscopy, sigmoidoscopy, and colonoscopy with biopsies, and prolonged immunosuppressive treatment required are likely to interfere with the quality of life of these patients.

Dr. Villalba also notes other potentially immune mediated SAEs in this SOC: celiac disease in subject **303/141-008** (for which she proposes that DAC may increase the risk in a patient with predisposition to autoimmune disease, and she notes 3 non-serious cases of celiac disease in the database), pernicious anemia in subject **303-439/007** with autoimmune gastritis, and an SAE of acute pancreatitis (303/613-005) that resolved but the patient developed diabetes mellitus (and 2 other cases of pancreatitis were identified by Dr. Villalba in patients with SAEs of colitis). Dr. Villalba also notes that some events of colitis were associated with non-GI immune disorder manifestations, and she considers that this may resemble and IPEX-like syndrome.

Dr. Villalba notes that it is sometimes difficult to distinguish between ulcerative colitis and Crohn’s disease, and that there are other conditions associated specifically with each of them (for example the risk of malignancy and primary biliary cirrhosis associated with ulcerative colitis, and sclerosing cholangitis associated with Crohn’s disease), although she notes that the management for ulcerative colitis and Crohn’s disease are similar. She does express concern that these conditions may be difficult to distinguish from other types of colitis or diarrhea that do not require system immunosuppression (and some that would not require invasive procedures in order to obtain a diagnosis).

Neurologic Disorders

This section will describe AEs in the Neurologic Disorders SOC, excluding MS or MS relapse. SAEs in this SOC (excluding MS) occurred slightly more frequently in DAC than in control in the controlled trials, as shown in the table below. Several TEAEs in this SOC occurred in at least 2%

of subjects on DAC and more frequently in DAC than in Interferon beta-1a in Study 301. These include seizures, including SAEs, for which in Interferon beta-1a labeling has a warning. I would include seizures in the label of DAC if it were to be approved. Several demyelinating events and 1 event of myasthenia gravis occurred on DAC; the role of DAC is not known but similar events with other immune modulators have been reported in the literature.

SAEs, Discontinuations, and TEAEs $\geq 2\%$ on DAC and at least as frequent as Interferon beta-1a in Study 301 in the Neurologic Disorders SOC

	Study 201			Study 301		Total DAC n=2236
	Placebo n=204	DAC 150 n=207	DAC 300 n=208	Interferon beta-1a n=922	DAC n=919	
SAEs (except MS)	0.5%	0.5%	1.4%	0.9%	1.5% ^a	1.4%
	Temporal epilepsy	Cerebrovasc insufficiency	Syncope Migraine Intracran, aneurysm	Seizures (0.2%)	Seizures (0.7%)	Seizures (0.4%) Headache (0.2%)
Discontinuations (except MS)	0%	0%	0.9%	0.3%	0.2%	0.4% (8 total, 4 nonserious)
TEAEs (except MS)^{b,c}	17.6	19.3	19.7	36.3	34.3	28%
Hypoaesthesia	-	-	-	5.9%	5.9%	4%
Dizziness	-	-	-	4%	5.3%	3%
Sciatica	-	-	-	1.2%	2.1%	2%
Seizures	-	-	-	0.3%	1.2%	0.5%

^a In addition to seizures included 1 each of dizziness, migraine, myasthenia gravis, sciatica, toxic encephalopathy, and transient ischemic attack (TIA), that did not occur on Interferon beta-1a (and 1 headache for DAC vs 1 tension headache for Interferon beta-1a).

^b Individual TEAEs are listed that occurred in at least 2% on DAC at least as frequently as Interferon beta-1a in Study 301. Seizures are also included for comparison to SAEs. (Individual Neurologic TEAEs did not occur in at least 2% of DAC in Study 201).

^c TEAEs related to MS relapse occurred in 38% of placebo, 23% of DAC 150, and 20% of DAC 300 in Study 201. TEAEs related to MS relapse occurred in 33% of DAC and 47% of Interferon beta-1a.

Dr. Villalba notes the imbalance in seizures (serious and non-serious) in Study 301 for DAC compared with Interferon beta-1a, a drug that has a Warning for seizures. Of the 6 subjects with seizure SAEs on DAC, Dr. Villalba notes that none had a history of seizures and in 4 cases the seizures did not appear related to worsening of MS; use of baclofen, that has seizures as a Warning, cofounded one case. Seizure SAEs on Interferon beta-1a occurred in subjects with worsening of MS. DAC may increase the risk of seizures in patients with MS, although the signal is not strong. If DAC is approved, I suggest including seizures in the labeling.

Cerebrovascular insufficiency on DAC in Study 201 in **Subject 201/509-017** who subsequently underwent angioplasty, vs none on placebo; 1 TIA on DAC in Study 301 (Subject **301/629-008** who had blood pressure of 168/85 on the day of the event; with arteriosclerosis; subject was treated with vascular therapy and improved; continued in study for approximately 1 year until completed) vs none on Interferon beta-1a. These cases do not appear to be related to DAC.

Cerebral venous thrombosis occurred in **Subject 303/659-001** who had risk factors of oral contraceptives and underlying sarcoidosis.

Other Neurological SAEs included 4 cases of headache; one case (**Subject 301/133-004**) had bilateral temporal headaches and underwent temporal artery biopsy to rule out temporal arteritis; she was treated with high dose prednisone and headaches apparently resolved while DAC therapy continued. Dr. Villalba considers that the case of aseptic meningitis (202/363-008), reported under the Infections SOC, could be an autoimmune disease potentially induced by DAC. In Total DAC, 13% of subjects had headache, the most common TEAE in this SOC in Total DAC.

Dr. Villalba notes demyelinating events: one case of tumor-like demyelination in a patients with an SAE of seizure (303/611-015) and a case of central pontine myelinolysis (202/509-014; JC virus negative; diagnosed by MR; sodium levels reportedly 138-146 mmol/L throughout the study⁹). Whether DAC played a role in the demyelinating events is not clear, but of note, a possible association of anti-TNF-alpha drugs that also are immune modulators with CNS demyelination has been reported in the literature¹⁰.

Subject 303/600-010 developed an SAE of myasthenia gravis beginning Day 997 of Study 301, treated with corticosteroids and neostigmine and a thymectomy; I note that other medications, for example ipilimumab, with immune effects have been associated with myasthenia gravis.¹¹ Whether DAC played a role in this case is unknown.

Lymphadenopathy¹²

Dr. Villalba has identified lymphadenopathy as a safety concern. There is an imbalance, particularly in SAEs and in TEAEs in Study 301 in particular. The increased frequency in Study 301 and in Total DAC reflect the longer duration of exposure in those pools. Because lymphadenopathy can be associated with variety of conditions from mild to serious processes requiring treatment, I recommend a discussion in the label.

SAEs, Discontinuations, and TEAEs of lymphadenitis, lymphadenopathy, or lymphoid tissue hyperplasia

	Study 201			Study 301		Total DAC
	Placebo n=204	DAC 150 n=207	DAC 300 n=208	Interferon beta-1a n=922	DAC n=919	n=2236

⁹ March 3, 20216 response to information request.

¹⁰ Andreadou E et al. Case Reports in Neurological Medicine Volume 2013 (2013), Article ID 671935, 9 pages <http://dx.doi.org/10.1155/2013/671935>

¹¹ Johnson DB et al. JCO November 20, 2015 vol. 33 no. 33 e122-e124

¹² Described in Dr. Villalba's review primarily under SAEs and Discontinuations in the *Blood and lymphatic system disorders* SOC

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

^a reflects 20 SAEs at the time of the SUR and 15 additional cases submitted subsequently.

^b reflects information only at the time of the SUR; 137 cases in Total DAC.

Dr. Villalba notes that most of the patients with these SAEs had brief hospitalization for diagnostic procedures. She notes that some cases were unresolved at the time of her review. Seven subjects had a biopsy or fine needle aspiration and Dr. Villalba notes that the pathology was consistent with benign reactive hyperplasia. Dr. Villalba notes that SAEs in this category were associated with the following processes:

- Infection (5) – and proposes that others may have been related to undiagnosed infection
- NHL (2)
- benign salivary neoplasm (2) – Dr. Villalba considers whether these could be Sjogren’s syndrome
- Skin reaction (3), thrombocytopenia (1), interstitial lung changes (several) – Dr. Villalba considers the possibility of a systemic reaction such as DRESS

Dr. Villalba notes that none of the SAEs in this SOC was diagnosed as sarcoidosis, but wonders how many had a workup to rule this out and believes that it should have been a consideration in several of the patients with hilar lymphadenopathy.

Psychiatric Disorders

There was no imbalance in SAEs in the *Psychiatric disorders* SOC in studies 201 or 301 (where SAEs of complete suicide/depression/depression suicidal/suicide ideation/suicide attempt were reported in 0.5% each in DAC or Interferon beta-1a). In the Total DAC database 6 subjects (0.3%) had SAEs of depression and 5 had SAEs of suicide attempt (0.2%). Dr. Villalba notes that most of the SAEs were in patients with a prior history of depression. There was an imbalance in the most common TEAEs in this SOC (Depression/Depressed Mood) that was greater in DAC than in placebo in Study 201 or in Interferon beta-1a in Study 301. I agree with Dr. Villalba that DAC should carry a Warning, as does Interferon beta-1a.

SAEs, Discontinuations, and TEAEs of Psychiatric Disorders

	Study 201			Study 301		Total DAC
	Placebo n=204	DAC 150 n=207	DAC 300 n=208	Interferon beta-1a n=922	DAC n=919	
SAEs	0%	0.5%	0%	0.9%	0.7%	0.7%
Discontinuations	0%	0%	0%	0.7%	0.1%	0.1%
TEAEs	5%	12%	17%	18%	18%	16%
TEAEs of Depression, Depressed Mood (combined)	2%	7%	7%	7%	10%	9%

Immune-mediated events

Dr. Villalba compiled a list of potentially immune mediated events. I will summarize information from the synthesized analysis in Section 8.5.3 of her review in addition to discussion of immune-related events in the SAEs and Discontinuations sections of her review. Events of acute hypersensitivity included angioedema (3.6% in Total DAC; 2.5¹³% on DAC vs 1.2% on Interferon beta-1a in Study 301), anaphylaxis, and serious urticaria. Acute hypersensitivity events occurred throughout the DAC treatment period and lasted up to at least 201 days. Regarding other inflammatory/immune/autoimmune events, considered individually it would be difficult to attribute 1 or more disparate AEs to a drug. However, grouped together, these DAC associated immune-mediated adverse events (in addition to those identified as skin disease) occurred in at least 28% of patients in Total DAC, affect most organ systems, and seem to have a biologically plausible basis that may be related to T cell dysregulation. Imbalances occurred in these grouped terms in Study 301, and in some individual terms including psoriatic conditions, sarcoidosis, vasculitis, and immune-related endocrine disorders related to thyroid disease and diabetes for which a role for DAC cannot be ruled out. Sometimes the events presented concurrently or sequentially in the same patient. I agree with Dr. Villalba that because of the immunologic effects of DAC, it may be inducing or unmasking immune mediated diseases. The immune-mediated events may require invasive procedures for diagnosis, prolonged immunosuppressive treatment, and that may impact quality of life. I would include a section of labeling in Warnings and Precautions to describe immune-related events. Because they are serious, some could be prevented with monitoring, and they may affect a patient's consideration for using DAC, I would consider a boxed warning.

In response to the 74 day filing letter, the sponsor submitted an analysis of allergic and autoimmune mediated events¹⁴. Dr. Villalba notes in Section 8.5.3 the deficiencies in that analysis that result in underestimation of the risk. This was revised in a March 8, 2016, response to a February 18, 2016, information request. In that response, the Sponsor reported that the risk of immune-mediated events (excluding eczema and dermatitis events) was 17% overall and was 18% for DAC vs 6% for Interferon beta-1a in Study 301. Dr. Villalba subsequently performed an additional analysis (after finalization of her review) as she refined her search strategy. In that analysis she finds that the frequency of immune-mediated events in the Total DAC database was 28%. In Study 301, the frequency of immune-mediated events was 32% on DAC vs 12% on Interferon beta-1a; SAEs of immune-mediated events were observed in 4% on DAC vs <1% for Interferon beta-1a. In Study 201, the frequency was 14% for DAC 150, 14% for DAC 300 and 8% for Placebo. The frequency of SAEs of immune-mediated events in Study 201 was 0.5% for DAC 150, 3% for DAC 300, and 0.5% for placebo.

Acute hypersensitivity events: Dr. Villalba identified 80 potential cases of angioedema in the Total DAC pool. In Study 301 Dr. Villalba identified 232 (2.5%) patients on DAC vs 11 (1.2%) on Interferon beta-1a with AE terms consistent with angioedema¹⁵. Dr. Villalba

¹³ From table 13.3.10 of Dr. Villalba's review; includes 23 subjects.

¹⁴ In response to FDA request (Response 5f) the sponsor conducted analyses of potentially immune-mediated reactions. Events under the MedDRA high level group term of allergic conditions, the high level group term of autoimmune disorders, or the high level term of colitis (excluding infective), including potentially inflammatory gastrointestinal reactions. The search did not include relevant terms such as sarcoidosis and alveolitis, and included unrelated terms such as seasonal allergy, and conducted the search based on preferred terms, not final diagnosis which because of miscoding as noted by Dr. Villalba could miss cases.

identified 6 subjects with events categorized as serious, severe, or leading to drug withdrawal that included angioedema and anaphylaxis, hypersensitivity in Section 8.5.3 of her review and additional cases elsewhere (although I am not convinced that **Subject 201/752-010**, identified as having” hypersensitivity, syncope, and circulatory collapse” is clearly a case of hypersensitivity¹⁶). These included cases of angioedema:

301/441-021 – non-serious angioedema 3 weeks after 8th dose resolved with prednisolone; SAE of angioedema 1 day after 9th dose; possibly related to insect sting or viral; “Rapid” response to oral steroids; stayed on DAC without further angioedema. I agree with Dr. Villalba that this is unlikely directly caused by DAC, although the subject later developed “allergic dermatitis” resulting in withdrawal.

301/552-014 – SAE of angioedema of 16 doses of DAC; 2 hours after taking Chinese herbal preparation, abated with desloratidine; angioedema approximately 6 months later, 1 hour after ibuprofen and diagnosed with NSAID intolerance. Continued treatment with DAC for total of 29 doses without further occurrence, but developed hypersensitivity pneumonitis.

202/765-013 – non-serious angioedema after 21 doses of DAC

203/306-001 – non-serious lip swelling, edema of mouth of moderate intensity with lymphadenopathy after 82 doses of DAC. (Previously, lip dyskeratosis and eczema after 20 and 36 doses of DAC, respectively). Treatment included oral prednisolone. Mouth edema, generalized rash resolved 4 months after DAC discontinuation.

301/703-004 – a non-serious event of lip swelling along with pruritus in patient with history of spongiotic dermatitis; 21 days after 2nd dose of DAC. Patient also had erythema, local swelling pruritus after 1st dose. Also taking ibuprofen. Lip swelling resolved 2 days later.

Other cases of acute hypersensitivity included:

201/458-007 had an event of “presyncope” associated with palpitations/weakness on the day of the first dose of DAC300 and rash the day after the first dose leading to drug withdrawal.

203-555-001 presented with rash, followed 3 days later by anaphylaxis¹⁷ (and angioedema) characterized by tongue swelling, hoarse voice, and almost fainted after 68 doses of DAC;

¹⁵ Angioedema-related terms included allergic edema, angioedema, eye swelling, eyelid edema, face edema, gingival swelling, lip swelling, edema mouth, periorbital edema, swollen tongue.

¹⁶ One dose of DAC is given as 3 subcutaneous injections. Subject 201-752-010 was identified as having “hypersensitivity, syncope, and circulatory collapse” after the first dose of DAC 300 and that Dr. Villalba considers consistent with hypersensitivity. His blood pressure 10 minutes after the first injection was 90/40 mm Hg. He did have circulatory collapse with BP as low as 70/10 and fainted within 15 minutes of the 3rd injection, requiring IV fluids and treatment with IV methylprednisolone; He stabilized after 30 minutes with a BP of 120/70 according to the narrative on p. 1558 of the study report. The narrative does not mention skin or mucosal involvement, respiratory compromise, or gastrointestinal symptoms, and it is not clear to me what caused the circulatory collapse or whether it is immune-related (perhaps it was vasovagal).and I wonder whether it could have been vasovagal syncope.

¹⁷ According to Kim and Fischer (*Allergy, Asthma & Clinical Immunology* 2011; 7 (Suppl 1):S6 doi:10.1186/1710-1492-7-S1-S6), criteria for anaphylaxis are a) Acute onset of illness (minutes to several hours) with involvement of skin or mucosal tissue or both (e.g. hives, pruritus or flushing, swollen lips or tongue) and at least one of the following: respiratory compromise or reduced blood pressure (or associated symptoms of end-organ dysfunction (e.g. hypotonia [collapse], syncope, incontinence) **OR** b) **2 or more of the following that occur rapidly after exposure to a likely allergen for that patient** (minutes to several hours): a. Involvement of

the subject, who had an episode of sarcoidosis 9 months prior to this event that resolved, was treated with an antihistamine and steroids, DAC was discontinued, and at the time of the report was still treated with oral corticosteroids.

303-136-002 – “hypersensitivity” reported after 8 doses of DAC, along with maculopapular rash that became severe and resulted in drug withdrawal. The narrative dose not describe the “hypersensitivity”.

303/557-005, hospitalized with acute urticaria after 37 doses of DAC, for which DAC was discontinued; the event was ongoing (along with eczematous dermatitis) 2 months later.

Acute hypersensitivity events occurred after 1 to 77 doses of DAC. These included at least 2 cases of angioedema for which a role for DAC cannot be ruled out (**203/306-001 and 202-765-013**), 1 case of anaphylaxis, and 1 case of serious urticaria that seemed related to DAC. In other cases other drugs appeared more directly involved, although those patients also had other immune reactions while taking DAC and it is plausible that DAC could have contributed. The case of anaphylaxis did not meet the definition of acute onset, but perhaps that is due to the long half-life of the drug, requiring time for sufficient levels to be achieved. Dr. Villalba notes that the events lasted 1 to at least 201 days. Given the long-lasting effects of DAC, I wonder about its role in short-lasting events; based on its very long half-life it is plausible that it could be responsible for long-lasting hypersensitivity events.

Dr. Villalba characterized *diseases of immune dysregulation/autoimmune diseases* in this database. The Sponsor finds 17% of DAC-treated patients with immune-mediated disorders overall, with 18% on DAC vs 6% on Interferon beta-1a in study 301 (excluding eczema and dermatitis). Dr. Villalba subsequently performed an additional analysis (after finalization of her review) as she refined her search strategy. In that analysis she finds that the frequency of immune-mediated events in the Total DAC database was 28%. In the Total DAC pool these included dermatitis/eczema (24%), lymphadenopathy (6%), psoriasis (2%), enteropathy (1.2%), immune-mediated hepatitis (0.5%), vasculitis (0.3%), sarcoidosis (0.3%), and celiac disease (0.2%). In Study 301, the frequency of immune-mediated events was 32% on DAC vs 12% on Interferon beta-1a; SAEs of immune-mediated events were observed in 4% on DAC vs <1% for Interferon beta-1a. In Study 201, the frequency was 14% for DAC 150, 14% for DAC 300 and 8% for Placebo. The frequency of SAEs of immune-mediated events in Study 201 was 0.5% for DAC 150, 3% for DAC 300, and 0.5% for placebo. Dr. Villalba notes that these immune-related diseases included organ specific diseases such as colitis, thyroiditis, rheumatoid arthritis, sometimes presenting concurrently or sequentially in the same patient. Dr. Villalba notes that some of the immune diseases are difficult to classify because of their overlapping clinical presentations. The mechanism for some of these conditions are not established¹⁸. I discuss specific types of inflammatory/immune/autoimmune diseases in the paragraphs below.

skin-mucosal tissue, b. Respiratory compromise (e.g., dyspnea, wheeze, bronchospasm, stridor, reduced PEF, hypoxemia), c. Reduced blood pressure or associated symptoms (e.g., hypotonia [collapse], syncope, incontinence), d. Persistent GI symptoms (e.g., painful abdominal cramps, vomiting)

¹⁸ Diamond, Betty, and Peter E. Lipsky. "Autoimmunity and Autoimmune Diseases." *Harrison's Principles of Internal Medicine, 19e*. Kasper D, Fauci A, Hauser S, Longo D, Jameson J, Loscalzo J. Kasper D, Fauci A, Hauser S, Longo D, Jameson J, Loscalzo J Eds. Dennis Kasper, et al. New York, NY: McGraw-Hill, 2015. n. pag. AccessMedicine. Web. 25 Feb. 2016.

<<http://accessmedicine.mhmedical.com/content.aspx?bookid=1130&Sectionid=79749895>>.

Hematologic disorders: SAEs that are or could be immune-mediated hematologic disorders included hemolytic anemia in 3 subjects (0.1%), all of whom had been on DAC for approximately 3 years; thrombocytopenia, ranging from mild to severe, and in some cases accompanied by other immune-mediated events, in 4 subjects; and a case of hemophagocytic syndrome. All cases required treatment with steroids and some required hospitalization and blood transfusion. I agree with Dr. Villalba that there is a biological plausibility for a role of DAC in immune mediated hematologic events, and that a role for DAC cannot be ruled out in these cases.

Hematologic parameters were measured every 4 weeks through week 40 in Study 201 and every 4 weeks up to week 24 and then every 12 weeks in Study 301. Platelet count of <75,000/mm³ (based on confirmatory tests 1 week apart) resulted in discontinuation from the study. Whether to include guidance regarding monitoring parameters in the labeling should be considered.

SAEs, Discontinuations, and TEAEs of Bleeding Related Hematologic Disorders

	Study 201			Study 301		Total DAC n=2236
	Placebo n=204	DAC 150 n=207	DAC 300 n=208	Interferon beta-1a n=922	DAC n=919	
SAEs	0%	0%	0%	0.2% ^d	0.5% ^c	0.6% ^{a, b}
Discontinuations	0%	0%	0%	0%	0%	0%
TEAEs (>2% and at least 1% greater than Interferon beta-1a in Study 301)						
Anemia	0.5%	2.9%	1.9%	3.0%	3.9%	5%

^a Includes anemia (2), hemolytic anemia (3), histiocytosis haematophagic, iron deficiency anemia (2), pernicious anemia, and thrombocytopenia (4).

^b Includes cases after the cutoff of the SUR

^c Includes anemia (1), iron deficiency anemia (1), hemolytic anemia (1), and thrombocytopenia (2)

^d Includes anemia (1), iron deficiency anemia (1)

There were 3 SAE of immune hemolytic anemia:

301/472-005 – Coombs positive hemolytic anemia, diagnosed 184 days after last dose. Had 36 doses of DAC. Hgb 72 g/L, considered NCI CTCAE grade 3 (severe) while on alternative treatment with interferon (which is associated with hemolytic anemia/TMA/HUS). Decrease in Hgb (to 80 g/L) noted 5 months after last dose of DAC (and 1 month after starting interferon). Hospitalized and treated with prednisone. Cannot rule out a role for DAC.

203/100-002 – Coombs positive hemolytic anemia, after 3.5 years of treatment with DAC. Hgb 3.4 g/dL (considered NCI CTCAE grade 4 [life-threatening or disabling]) in the setting of a UTI that was treated with pantoprazole, cefoperazone and sulbactam

Levinson, Warren. "Tolerance & Autoimmune Disease." *Review of Medical Microbiology and Immunology*, 13e. Levinson W. Levinson W Ed. Warren Levinson. New York, NY: McGraw-Hill, 2014. n. pag. AccessMedicine. Web. 25 Feb. 2016. <<http://accessmedicine.mhmedical.com/content.aspx?bookid=1023&Sectionid=57053513>>

(hemolytic anemia has been reported with sulbactam and cefoperazone). Required transfusion of PRBC and treatment with prednisone. Cannot rule out a role for DAC.

302/463-103 - Coombs positive hemolytic anemia. Presented with conjunctival jaundice after 35 doses of DAC HYP; She felt dizzy and had a syncopal episode. No concomitant medications. Hb 74 g/l (NCI CTCAE grade 3 [severe]). Hospitalized and treated with steroids.

There were 5 SAE of thrombocytopenia:

301/480-002 - one month after the last dose of DAC 150 (which was on Day 305), platelets $58 \times 10^9/L$ (NCI CTCAE grade 2 [moderate]) leading to drug withdrawal. Events lasted one week without specific treatment. Confounded by carbamazepine and diclofenac. Given the time course of resolution, does not seem likely related to DAC.

301/670-017 – treated with DAC for more than 2 years. Event occurred 1 month after last dose and was accompanied by rash that began 1 month later. Anti-platelet antibody tests were negative according to the study report for Study 301. Platelets as low as $23 \times 10^9/L$ (NCI CTCAE grade 4 [life-threatening or disabling]), reportedly without signs or symptoms of thrombocytopenia. No concomitant medications. Required treatment with prednisone and took 7 months to resolve (reportedly not compliant with prednisone). Dr. Villalba notes that the SUR states this subject had HIV-induced thrombocytopenia.

301/617-003 – Platelets down to $80 \times 10^9/L$ (NCI CTCAE grade 2 [mild]) with anemia and lymphadenopathy. History of bladder neoplasm. Suspected viral infection, and melanoma metastases in kidney.

303/649-009 – Hypothyroidism on Interferon beta-1a in Study 301. Autoimmune hepatitis after 4 doses of DAC150 in Study 303. DAC discontinued. Responded to corticosteroid treatment. Developed thrombocytopenia when corticosteroids were tapered, approximately 4 months after discontinuing DAC. Thrombocytopenia was treated with corticosteroids and resolved.

203/906-005 – Nasal hemorrhage and hemorrhagic rash after 67 cumulative doses of DAC 150 mg (44 days after last dose). Hgb 92 g/L ((NCI CTCAE Grade 2 [moderate]); platelets not reported. Abdominal ultrasound showed splenomegaly. Hospitalized and treated with prednisone and etamsilate (a hemostatic drug). Final diagnosis of thrombocytopenic purpura and post- hemorrhagic anemia

Subject **203/303-005** had hemophagocytic syndrome in association with multiorgan failure in the setting of septicemia but in absence of a clear infectious agent; Dr. Villalba notes that hemophagocytic syndrome has been reported in the context of sepsis as well as with use of immunosuppressors.

For a further discussion of hematologic events please refer to the discussion of laboratory analyses.

Endocrine disorders : SAEs in the this SOC occurred in 0.2% of subjects in the Total DAC pool with no excess in DAC compared to placebo or Interferon beta-1a in Study 201 or 301. There were 4 thyroid related SAEs on DAC (1 in 301 vs 1 on Interferon beta-1a):

Autoimmune thyroiditis in **Subject 201/752/012**; began 20 days after the last DAC dose and lasted for 7 days

Thyrotoxicosis¹⁹ and ketoacidosis in **Subject 301/327-005** with a history of a goiter

¹⁹ Also known as Graves' disease or Basedow's disease; an autoimmune disorder.

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Basedow's disease in Subject 202/765-003
Benign neoplasm of thyroid gland/goiter (Subject 203/563-001).

Diabetes-related SAEs occurred as follows:

New onset Type 1 diabetes in 301/327-005; Diabetes mellitus in 303-438-001 (who had a history of diabetes);(coded also under Metabolism and Nutrition disorders; none on Interferon beta-1a)
Type 1 diabetes as well as DILI, eczema, and toxic pancreatitis in subject 303/667-017 that Dr. Villalba notes is consistent with IPEX-like syndrome
Diabetes insipidus in Subject 201/903-02; Dr. Villalba notes that this can be immune mediated.

The onset of the Endocrine SAEs occurred 14 to 1190 (mean 405) days into treatment. There is some evidence in the literature that some autoimmune thyroid disease co-occurs in patients with MS to a greater extent than in the general population and similarly for diabetes²⁰; the relationship of these immune-related endocrine events to DAC is not known.^{21,22}

Gastrointestinal disorders: Please refer to my discussion on pages 27-29, above.

Musculoskeletal and Connective Tissue: SAEs in this SOC occurred in 0.7% of the Total DAC database and Dr. Villalba notes an additional case reported after the cutoff of the SUR. There were no SAEs in this SOC for DAC in Study 201. In study 301 there were 6 (0.7%) for DAC and 3 (0.3%) for Interferon beta-1a. Dr. Villalba describes the following potentially immune mediated events:

Lupus-like syndrome with myalgia, arthralgia, cutaneous lesions and adrenal insufficiency in subject **301/482-005** after 24 doses of DAC
Spondyloarthropathy that occurred after 51 doses of DAC in subject **301/604-006** who may have been predisposed to autoimmunity with a history of psoriasis and hyperthyroidism and for which DAC was not discontinued
(Neither of which occurred on Interferon beta-1a in Study 301)
Adult Still's disease, a systemic inflammatory disease after 21 doses of DAC in Subject **303/645-015**
Inflammatory arthritis (and rash) in subject **303/658-012**; after 23-29 doses of DAC.

Neurologic: see SAEs of aseptic meningitis (*under Infections*) and myasthenia gravis (*under Neurologic disorders*) above.

Renal and Urinary Disorders: 2 SAEs of glomerulonephritis discussed under this SOC, in Other Serious Adverse Events, below.

Respiratory, Thoracic and Mediastinal Disorders: SAEs in this SOC occurred in 0.6% in the Total DAC database. There were no SAEs in this SOC in Study 201; Dr. Villalba reports more events in the DAC 150 group (6/919, 0.7%) than in Interferon beta-1a (1/922, 0.1%) in Study 301.²³ Dr.

²⁰ Wertman E, Zilber N, and Abramsky O. [J Neurol](#). 1992 Jan;239(1):43-5.

²¹ Sloka JS et al. *J Autoimmune Dis*. 2005; 2: 9. Published online 2005 Nov 9. doi: [10.1186/1740-2557-2-9](https://doi.org/10.1186/1740-2557-2-9)

²² [Niederwieser G](#) et al. [J Neurol](#). 2003 Jun;250(6):672-5.

²³ In addition to the immune-mediated events, there were other SAEs in this SOC. There were 3 case of

Villalba notes at least 7 (0.3%) SAEs consistent with immune mediated lung disease in Total DAC (9 SAE if 3 patients with atypical pneumonia described under infections are included). She raises a concern, based on cases with mediastinal or hilar lymphadenopathy, about an immune mediated disease such as sarcoidosis. The 7 SAEs are:

Pulmonary sarcoidosis in subject **303/611-029**

Interstitial pulmonary nodules and hilar lymphadenopathy in subject **303/609-013**

Alveolitis and pulmonary fibrosis in subject **203/563-001**

Interstitial lung disease in subjects **301/457-001** and **203/751-015**

Pulmonary granuloma (miliary lung nodules and mediastinal lymphadenopathy) in Subject **301/554-001**

Interstitial lung disease with cutaneous nodules that showed non-caseating granulomas and hilar lymphadenopathy (that Dr. Villalba states is therefore sarcoidosis) in subject **302/622-502**

I note that on February 8, 2016, the Sponsor submitted additional cases of sarcoidosis in response to an information request of February 1, 2016. In addition to a possible serious case (303/622-106), the Sponsor has identified the following cases of sarcoidosis:

Serious:	303/611-029	302/622-502
	303/325-001	
Non-serious:	203/555/001	302/463-105
	303/659-001	303/622-106
	303/659-014	

Dr. Villalba discusses sarcoidosis, and provides support for biological plausibility of a relationship to DAC as sarcoidosis is characterized by T cell activation. She notes that sarcoidosis can be benign or life-threatening and can lead to irreversible pulmonary fibrosis and blindness if not treated adequately and that definitive diagnosis may require invasive procedures. In the Total DAC pool, Dr. Villalba finds 9 diagnosed cases of sarcoidosis listed by the Sponsor (including 3 pulmonary; none in a controlled trial) and at least 4 others suggestive of sarcoidosis. She notes that 6 of the 9 cases were reported after the cutoff of the SUR, suggesting that a long exposure is need for sarcoidosis to develop, or offering an alternative explanation that perhaps it is more difficult to diagnose. Dr. Villalba states that there is no definitive laboratory test, but that calcium is often elevated because sarcoidosis is characterized by the presence of granulomas, and granulomas produce vitamin D. She notes that although calcium is a routine test that should be part of any chemistry profile, it was not measured or reported in this database.

The Sponsor calculates the rate of sarcoidosis, based on 9 cases, as 1.32/1,000 [CI 0.62-2.57] person years as of January 31, 2016. They believe that is within the background rate in an MS population (1.73/1,000 patient years) from the Impact claims database (a rate which they claim is 4X higher in the MS population vs the general population control in that database. The FDA Division of Epidemiology, in a review by Dr. Elisa Braver dated March 10, 2016, found the Sponsor's report inconclusive because of flaws in the methods for analyzing the insurance claims database. Dr. Villalba cites a rate in the general population of 1 to 35.5 per 100,000 per

pulmonary embolism on DAC but all 3 patients had risk factors and it is not possible to determine the contribution of DAC. One SAE of aspiration pneumonia was reported in this SOC (in addition to the 2 cases under Deaths in patients with advanced MS).

year. She notes the postmarketing estimated rate of sarcoidosis in several approved MS drugs that is much lower than the rate in the DAC database.

Skin disorders: Immune related skin disorders include psoriasis and eczema, cutaneous vasculitis, panniculitis (inflammation of subcutaneous fatty tissue), and vitiligo. Please refer to my discussion on beginning on page 23.

Systemic Inflammatory Syndrome with Multiorgan failure: Dr. Villalba identified 3 cases in the database that she considers to be DRESS (203/901-006 reported as SJS but not considered to be SJS by the Central Dermatologist, and 301/512-006 and 303/512-009). Regiscar Criteria for DRESS²⁴ are a standard classification for diagnosis of DRESS and are as follows:

Required: Hospitalization
 Suspected to be Drug-related

And 3 of 5 of the following:

- Rash
- Fever
- Lymphadenopathy in at least 2 sites
- Involvement of at least 1 internal organ
- Blood count abnormalities (such as eosinophilia)

	Hospitalization	Fever \geq 38.5°C	Enlarged Lymph nodes in at least 2 sites	Eosinophilia	Rash	Organ involvement
203/901-006 ²⁵	✓ ²⁶	x	✓	Eosinophils	✓	Goiter

²⁴ Kardaun SH. J AM Acad Dermatol 2014:1000.

	(but expert dermatologist thought based on photographs of the rash that hospitalization would not have occurred in US)			25%	(scaling, desquamation; described on legs and arms but trunk did not have rash so not clear if it covered > 50% of BSA; lip swelling but facial edema not described)	identified; some cardiac involvement but relevant cardiac history prior to enrollment.
301/512-006	✓ (for plasmapheresis)	x	x	²⁷ x	✓	X ²⁷
303/512-009	Only brief hospitalization for plasma exchange	x	x	²⁸ x	✓	ALT increased; not clear if related ²⁹

Although all 3 had rash and met some of the criteria, only 203/901-006 possibly met all of the criteria for possible DRESS (except for possibly hospitalization). Hospitalization in 2 cases was for a procedure such as plasmapheresis but not for the event and in 203/901-006 the Central Dermatologist did not think hospitalization would have occurred in the US based on his review of the photographs of the rash; 2 of the 3 did not have documentation of 3 of the 5 criteria. Although I do not believe they can be called DRESS, (the Central Dermatologist, ^(b)₍₄₎) considered that 203/901-006 could be acute generalized exanthematous pustolosis, or other drug hypersensitivity reaction but did not refer to it as DRESS), I would agree that they all are an example of a multi-organ systemic condition. Even if 203/901-006 could be a possible case of DRESS, identifying this as a multiorgan inflammatory reaction in the label would not impact appropriate treatment of the individual components of such a reaction.

Dr. Villalba considers several events in this category, considering sepsis vs. immune mediated. These include **Subjects 203/303-005** with hemophagocytic syndrome and **303/645-015** with adult Still’s disease discussed previously in my memo, and **303/552-001** with multi-organ failure/sepsis of unknown origin that she suspects could be immune mediated systemic reactions. She also believes that SAEs in subjects **301/606-020** with multiorgan failure, and evidence of systemic vasculitis with suspected sepsis but without identification of an

²⁵ Evaluation using the scoring criteria provided in Roujeau JC et al (Dermatol Sinica 27:230-209, 2009) or Kardaun SH J Am Acad Dermatol; 71 (5), 2014: suggest that this could be a possible case or not a case (depending on the extent of skin involvement and whether morphology is suggestive for DRESS); In an email of 5/19/16 Dr. Villalba considers whether it is consistent with SLE given a positive ANA.

²⁶ Central Dermatologist commented that based on severity of the rash in the photographs, it was unlikely this person would have been admitted to the hospital in the US and said this was a likely hypersensitivity reaction to daclizumab.

²⁷ Dr. Villalba’s review mentions mild pancreatitis and eosinophilia. However, Central dermatologist said no internal organ involvement. There is no evidence of pancreatitis or eosinophilia in the labs in the patient profile. In an email communication of 5/19/16 Dr. Villalba could not confirm pancreatitis and eosinophilia.

²⁸ Dr. Villalba’s review notes eosinophilia in June 2014. However, narrative only mentions eosinophilia in October, and the expert Dermatologist says that eosinophilia did not occur during the course of the event. In an email from 5/19/16, Dr. Villalba could not confirm the eosinophilia during the event.

²⁹ Increased ALT approximately 2 months after rash and may have been due to pulse steroids.

organism, **303/453-048** with brucellosis, and **303/609-013** with peripheral edema, generalized eczema, lymphadenopathy, and lung disease, DRESS) may have been caused by an immune mediated systemic inflammatory reaction. The diagnosis of brucellosis was based only on positive IgM serology and response to antibiotics, and the subject had a complicated clinical course including elevated liver enzymes that Dr. Villalba believes may be attributed to a systemic inflammatory reaction rather than to brucellosis.

Other Serious adverse events

SAEs in the *Injury, Poisoning, and Procedural* SOC occurred in 26 of 2236 (1.2%) in the Total DAC group. There was no imbalance for DAC in either Study 201 (1% for placebo, 0.5% for DAC 150, and none for DAC 300). There was no imbalance in Study 301 (0.9% for Interferon beta-1a, 1.2% for DAC). In Study 301 the SAEs were driven by fractures and falls that I note occurred to a greater degree in DAC than in Interferon beta-1a. However, Dr. Villalba notes that falls and fractures are not unusual in patients with MS. She also notes that there are no calcium, phosphorous, or magnesium measurements in the protocols to evaluate whether fractures were related to abnormalities in these measurements.

SAEs in the *Reproductive System and Breast Disorders* SOC occurred in 1.1% of females in the Total DAC database, excluding malignancies. There was no imbalance overall in studies 201 or 301, although the SAEs showed that eleven patients had some kind of uterine disorder including endometriosis, endometrial disorder, endometrial hypertrophy, adenomyosis, uterine hemorrhage, several of which occurred in Studies 201 (n=2) and 301 (n=3) but that were not observed in placebo or in Interferon beta-1a in Studies 201 or 301, and Dr. Villalba notes this raises a question of whether there is an effect of DAC on endometrial function.

SAEs in the *Surgical and Medical Procedures* SOC occurred in 0.4% of subjects in the Total DAC pool and Dr. Villalba notes that none represent procedures done in the context of evaluation of AEs that developed during treatment with DAC. However, she does note a variety of surgical and medical procedures that were performed due to DAC-related AEs but were not recorded here including 8 subjects with liver biopsy, 12 with colonoscopy /biopsy for work-up of colitis-related terms, various other biopsies, lymphadenectomies, plasmapheresis, blood transfusions, and intubation. I agree with her that these invasive procedures, with associated morbidity, are likely to interfere with quality of life and may undermine potential benefits of DAC.

SAEs in the *Renal and Urinary Disorders* SOC occurred in 0.4% of subjects in the Total DAC pool. Overall, Dr. Villalba notes no imbalance in the controlled trials. However, she does note 3 SAEs of nephrolithiasis and one of renal colic with DAC vs 1 urinary calculus with Interferon beta-1a in Study 301, suggesting a possible increased risk with DAC, although the number are small and there is no supportive laboratory data with respect to calcium, phosphorous, or uric acid levels. This would be an issue to monitor in the future. There were 2 cases of glomerulonephritis (202/505-018 with mesangioproliferative glomerulonephritis and nephrotic syndrome and 203/500-002 with glomerulonephritis and nephrotic range proteinuria. In an email of January 21, 2016, Dr. Evelyn Mentari, a nephrologist on the DNP Safety Team, concluded that these cases could be related to DAC. She noted that the proteinuria was severe at the first abnormal protein measurement, although she noted that the frequency of urine testing was variable and often infrequent. She recommended that if DAC is approved, urinalysis (with quantitative protein) using

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first morning urine should be obtained every 3 months. If positive (>20 mg/dL), this should be followed up with a 24 hour urine protein.

SAEs in the *Metabolism and Nutrition Disorders* SOC occurred in 6 (0.3%) subjects in the Total DAC pool. There was no imbalance in Study 201. In Study 301, 4 DAC subjects (0.4%) vs none on Interferon beta-1a had SAEs in this SOC. These included dehydration that occurred with toxic hepatitis, and hypokalemia that occurred with vomiting and diarrhea, and “tetany” associated with influenza (**301/663-007**) in a subject routinely taking calcium. One SAE each of diabetes mellitus and ketoacidosis (**301/327-005**) was mentioned under the Immune-mediated diseases/*Endocrine disorders* SOC.

SAEs in the *Cardiac Disorders* SOC occurred in 6 (0.3%) subjects in the Total DAC Pool. Dr. Villalba finds no excess in DAC vs placebo or Interferon beta-1a. In the DAC group there were 2 cases of cardiomyopathy (**303/554-00**, resolved after 6 days, in a patient with hypertensive heart disease; **303/433-003** who had possible etiologic factors of myocarditis following recent vaccination vs suspected MI 6 months prior to the diagnosis vs DAC-related) and I agree with Dr. Villalba that it is difficult to attribute these to DAC.

SAEs in the *Vascular Disorders* SOC occurred in 0.4% of subjects in the Total DAC pool. SAEs not already mentioned elsewhere are as follows. In Study 301 there were 4 SAE on DAC: one DVT, one hypotension (301/128-003, beta-blocker overdose), and 2 vasculitis. Two SAEs of DVT were reported in the Total DAC database; they resolved and did not lead to discontinuation and Dr. Villalba notes that DVT would not be unusual in patients with MS who have limited mobility.

SAEs in the *Pregnancy, Puerperium and Perinatal* SOC occurred in 4 subjects (0.2%) of the Total DAC pool: 3 spontaneous abortions and 1 ectopic pregnancy (vs 1 missed abortion on placebo and 1 spontaneous abortion on Interferon beta-1a). I agree with Dr. Villalba no conclusions can be made regarding the role of DAC.

SAEs occurred in 3 subjects (0.1%) in the *Ear and Labyrinth Disorders* SOC (I agree that the cases of vertigo and acute vestibular syndrome may have been manifestations of MS) and in 1 subject in the *Congenital* SOC in the Total DAC pool (dermoid cyst) and there is no indication that these are related to DAC. In the *Eye Disorders* SOC Dr. Villalba notes a case of iritis could be a manifestation of autoimmunity; in that respect it could be either related to MS or to DAC.

Significant Adverse Events

Dr. Villalba identifies few events graded as severe and they only occurred in more than 2 subjects each in Study 201 (in the DAC groups these included 4 patients with muscle spasms in DAC 300, 2 patients with vomiting on DAC 300, and 2 with pruritus on DAC 300). She notes findings that analysis by severity did not identify any relevant AEs not previously identified by review of SAEs or discontinuations.

Treatment Emergent Adverse Events and Adverse Reactions

Dr. Villalba shows that the SOCs with the most AEs (and greater than placebo in Study 201, at least the same as Interferon beta-1a in Study 301) were Infections and Infestations, Nervous system Disorders excluding MS in Study 201, General Disorders in Study 201, Skin and Subcutaneous Tissue Disorders, Musculoskeletal in Study 301, and Gastrointestinal, all with at least 30% of patients have an AE in the DAC group in Study 301.

Dr. Villalba provides tables of the most common AEs (greater than 2% and at least 1% greater than comparator) in Studies 201 and 301 in the Appendix of her review. The following information is extracted from those tables, except where I indicate otherwise. Dr. Villalba notes that the percentage of patients with at least 1 AE was greater in Study 301 vs 201 consistent with a longer duration of treatment in 301. In Study 201, there appears to be a dose response relationship for many AEs.

The adverse events, excluding MS relapse, most commonly reported $\geq 5\%$ in any DAC group) and greater than placebo in Study 201 were:

Body System or Organ Class	Adverse Event	Placebo N=204 % ^b	DAC 150 N=208 % ^b	DAC 300 N=209 % ^b
Infections and Infestations	Respiratory Tract Infection	8	7	11
	Upper Respiratory Tract Infection (URI), URI viral	7	9	10
	Pharyngitis	4	6	6
	Oral Herpes	5	5	6
	Influenza	5	2	6
	Urinary Tract Infection	4	4	5
General Disorders and Administration Site Conditions	Pyrexia	1	3	7
Psychiatric Disorders	Depression, Depressed Mood (combined)	2	7	7
Investigations	ALT increased	2	5	6
Skin and Subcutaneous Tissue Disorders	Rash ^a	1	7	7
	Dermatitis- and Eczema-Related Terms ^b	2	3	6

^a I combined rash, rash macular, and rash maculopapular from Table 35 of the report for Study 201 consistent with the Sponsor's grouping in the report for Study 301.

^b I combined eczema, dermatitis, dermatitis allergic, dermatitis atopic, and seborrheic dermatitis, and dyshidrosis from Table 35 of the report for Study 201, consistent with the Sponsor's grouping in the report for Study 301.

^c Values of 0.5 rounded to even number.

The adverse events, excluding MS relapse, most commonly reported ($\geq 5\%$ in any DAC group) and \geq Interferon beta-1a in Study 301 were:

Body System or Organ Class	Adverse Event	Interferon beta-1a N=922 %	DAC 150 N=919 %
Infections and Infestations	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 ^a	Dermatitis- and Eczema-related terms	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 (combined)	7	10
General Disorders and Administration Site Conditions	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	Hypoesthesia	6	6
	Dizziness	4	5
Blood and Lymphatic System Disorders	Lymphadenopathy	0.8	5

^a The terms reported here are from Table 219 of the study report for Study 301 and combine multiple terms. Dr. Villalba provides the same findings from the JumpStart Team with additional terms in this SOC that occurred in < 5% but with a $\geq 3\%$ risk difference or $\geq 3x$ Relative risk in DAC vs Interferon beta-1a including, angioedemas, bullous conditions, dermal and epidermal conditions, exfoliative conditions, papulosquamous conditions, photosensitivity and photodermatoses, and psoriatic conditions.

In the *General Disorders* SOC, Dr. Villalba notes no difference between DAC and placebo in the incidence of influenza like illness in Study 201. However she notes an excess of influenza-like illness on Interferon beta-1a (34%) compared to DAC (9%) in Study 301 and this occurs within the first 3 months, thus possibly unblinding the patients. She finds a similar incidence of injection site reactions for Interferon beta-1a and DAC, except for injection site hematoma and hemorrhage that were slightly higher in DAC. She also reports the Pain and discomfort HLT greater in DAC (7%) vs Interferon beta-1a (5%), and peripheral edema was greater in DAC (2%) than Interferon beta-1a (1%).

Dr. Villalba conducted analyses of AE with a cutoff at 180 days post-last dose (the cutoff used in the submission) vs 30 days post-last dose for Study 301, given the long-term effects of

DAC. She found no differences in the overall number of AEs, but captured a slightly greater percentage of SAE using the original 180 day cutoff (24%) compared to the 30 day cutoff (21%) in Study 301. These findings confirm that serious events continue to occur up to 180 days of last dose, and I agree that labeling should advise prescribers and patients of this if this drug is approved.

Some common AE terms, such as various types of similar skin reactions, should be combined (instead of split) in the presentation of common AEs in the label if this drug is approved.

Laboratory Findings

Please refer to Dr. Villalba's review of laboratory findings. She does not find differences between DAC and placebo or between DAC and interferon for hematology or chemistry parameters (except for liver-related findings). Glucose was not routinely measured and therefore may have underestimated diabetes mellitus. Calcium was not routinely measured which could have implications for diagnosis of sarcoidosis.

Hematology: Dr. Villalba finds no clear effect on total WBC. She finds a slight lymphopenia compared to placebo in Study 201, but similar to Interferon beta-1a in Study 301 (4% for DAC vs 2% for Interferon beta-1a), and a 5-7% decrease in Total DAC. She points, however, that the subset of lymphocytes affected by DAC may be different from those affected by Interferon beta-1a. NK cells were increased by 48% from baseline for DAC and 3% for placebo in Study 201. Neither CD4+ counts nor grade of lymphopenia or neutropenia decreased appeared to predict severity of infections.³⁰

In Studies 201 and 202, the Sponsor conducted analyses of *lymphocyte subsets*, showing a decrease in Tregs and an increase in NK cells. Dr. Villalba notes that the sponsor does not find a correlation between Treg levels and adverse events (or therapeutic efficacy); I agree with her that those findings do not allow a conclusion that Tregs are functional as the Sponsor asserts.

There was no increase in the number of eosinophils in DAC vs either placebo or Interferon beta-1a, but there was an increase in eosinophil counts by 30% from baseline by week 144 and by 80% by week 264 in the Total DAC database (but increases in individuals seemed to be generally isolated events as noted by Dr. Villalba). According to a February 16, 2016, response to an information request, the majority of AEs associated temporally with eosinophils > 7% were rash or other cutaneous events.

There was a 20% increase in monocytes and basophils in the Total DAC database and Dr. Villalba notes that the clinical significance of these increases is not clear.

Mean decreases in hemoglobin and platelet counts of approximately 2% from baseline occurred in the Total DAC pool. Decreased hemoglobin ≤ 100 g/L occurred in 4% of subjects and decreased platelets $\leq 100 \times 10^9/L$ occurred in < 1% including 5 subjects with platelet count less than $50 \times 10^9/L$. Grade 3 or more decreased hemoglobin (< 80 g/L) did not result in severe anemia, and Grade 3 or more decreased platelets (< $50-25 \times 10^9/L$) did not result in

³⁰ Based on February 1, 2016, response to an information request.

abnormal bleeding, hematoma, or hemorrhage in subjects included as of the SUR cutoff of November 14, 2014. However, as noted in the discussion of Immune-mediated hematologic events, above, there were several subjects after that time (or beyond the cutoff of 180 days after the last dose of DAC) with Grade 3 or more decreases in hematologic parameters that did have serious events requiring hospitalization or transfusion.³¹

Chemistry: Dr. Villalba does not find important differences between DAC and placebo or Interferon beta-1a for the chemistry laboratories (except for liver-related lab values). However, she notes that clinical studies did not include measurement of blood glucose, calcium, phosphate, or uric acid in the controlled studies or their extensions (except for calcium and glucose in study 302, a 6 month open label study in 113 subjects). I discuss implications of that omission elsewhere in my memo.

Please refer to Dr. Villalba’s review for detailed discussion of outlier analyses of ALT and concomitant elevation of ALT and bilirubin and to my memo under *Submission Specific Safety Issues*.

BUN and Creatinine – Dr. Villalba notes small increases in BUN and creatinine in Total DAC that remained stable throughout the study and notes that the changes could have been due to slight decreases in renal function or could have been due to dehydration. I agree that without a comparator this is difficult to interpret.

Thyroid function tests: In study 201, Dr. Villalba notes that thyroxine (T4) showed shift to low values in 5% of DAC 150 and DAC 300 and 3% of placebo. In Study 301, 12% of subjects on DAC vs 9% on Interferon beta-1a had a shift to low total thyroxine levels; 8% on DAC vs 5% on Interferon beta-1a had shift to low TSH. In The Total DAC pool, Dr. Villalba the following results:

	Shift to Low	Shift to high
TSH	6%	4%
Total Thyroxine	10%	5%
Free Thyroxine	2%	8%

Overall, for Total DAC, subjects with concurrent low TSH with either low or high thyroxine on the same day was similar as was the percentage of subjects with high TSH and low or high T4 on the same day (1% or less).³²

Dr. Villalba notes that similar numbers of patients had thyroid related AEs in study 301 in both groups (3 subjects in each group). These were 2 subjects in each group with autoimmune thyroiditis and 1 in each group with Basedow’s disease.

³¹ In a Submission of February 1, 2016, the sponsor responded to a request to provide a listing of all patients with hematologic parameters meeting the definition of NCI CTCAE ≥ 3 and to identify any associated adverse event. The Sponsor states “AEs reported during the month window around events of Gr3 decreased hemoglobin included and anemia (all nonserious; none severe). However, the safety cutoff was 180 days after the last dose of DAC. That would explain why subject **301/472-005** with Coombs positive hemolytic anemia and Grade 3 Hgb 184 days after last dose was not identified.

³² February 16, 2016, response to information request.

Urinalysis: Dr. Villalba notes a shift from negative to non-negative for *blood in urine* for 30% of DAC 150, 44% on DAC 300, and 36% on placebo in Study 201. In Study 301 she finds such shifts in DAC (in approximately 10% of subjects) slightly more frequently than in Interferon beta-1a at specific time points, and she finds shift to high in 27% in the Total DAC pool. She notes that it is difficult to interpret these findings in isolation, without quantitative values, or knowing whether it was associated with other signs or symptoms.

Dr. Villalba finds shifts to high for *urine protein*. Shifts from negative to non-negative were similar between DAC (43% and 48% for DAC150 and 300, respectively) and placebo (42%) in Study 201; shifts to high were similar between DAC (60%) and Interferon beta-1a (55%) in Study 301. In the Total DAC pool, 63% had a shift to high/positive. Sixty-one % of the shifts to high were trace and “1+”. No AEs of edema or diabetes were associated with proteinuria.²⁵

Urine glucose: Dr. Villalba finds slighter higher frequency of shifts from negative to non-negative in DAC (about 2-3%) vs placebo (1.5%) in Study 201. About 1% of subjects on DAC or Interferon beta-1a had abnormal urine glucose in Study 301. In the Total DAC pool 4% of subjects had glucosuria at least once, although 70% who developed glucosuria had only 1 abnormal reading.²⁵ Of the 82 who had glucosuria, 18% had a history of diabetes at screening and 60% were treated with high dose corticosteroids. Ten subjects had AEs temporally associated with glucosuria and most were hyperglycemia. One subject, previously discussed, had a SAE of diabetic ketoacidosis with thyrotoxicosis.

Vital Signs

Dr. Villalba reports that there were no clinically relevant changes in mean and median values for vital signs before and after dosing and at the end of the study for individual pivotal studies or the Total DAC database. Orthostatic changes were not measured.

Electrocardiograms (ECGs)

Dr. Villalba finds no relevant changes in phase 1, 2, or 3 trials of DAC. A thorough QT study was not performed.

Immunogenicity

Dr. Villalba notes that, according to the Summary of clinical Pharmacology Studies, treatment emergent anti-DAC antibodies (ADAs) were observed in 4% of evaluable subjects in study 201 and 19% in study 301. Neutralizing antibodies (Nabs) were observed in 3% of subjects in study 201 and 8% in 301. The higher incidence of immunogenicity in Study 301 was explained by more frequent testing at early time points and use of a more sensitive assay. Dr. Villalba notes that the majority of subjects who became ADA- positive did so during the first year of treatment and the immunogenicity response was transient. Dr. Villalba notes, and has noted throughout her review, there does not seem to be a correlation between present of ADA or Nabs and SAEs or AEs causing drug discontinuing, but that if high DAC levels interfere with detection of Nab, as noted by Chen Su, CMC/Product Quality reviewer, that a correlation would not be reliable.

Additional Safety Explorations

Human Carcinogenicity or Tumor Development

Please refer to discussion of Malignancies.

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Human Reproduction and Pregnancy

Please refer to summary of pregnancy outcomes in SAEs. There is too little data to allow conclusions regarding an effect of DAC on human reproduction and pregnancy.

Pediatrics and Assessment of Effects on Growth

Not evaluated in the pediatric population in this submission.

Overdose, Drug Abuse Potential, Withdrawal, and Rebound

The Sponsor concludes that there is a lack of signal for abuse or dependence properties in nonclinical and clinical studies. I do not find terms related to abuse or dependence among the common AEs (>2%). Dr. Villalba notes that at the pre-BLA meeting CSS agreed there is no need to conduct a study for assessment of abuse potential.

Concerns identified through U.S. or foreign postmarket experience

DAC is not yet marketed in the US or in the rest of the world. Dr. Villalba points out that safety data from daclizumab Nutley (Zenepak) used in the transplant population in patients receiving other immunosuppressive drugs and with different treatment regimens does not necessarily predict safety of DAC in the MS population.

Potential safety issues that could cause concern when considering how the drug may be used in the postmarket setting

Even under conditions of stringent monitoring and evaluation of liver enzymes, cases of severe DILI are likely to occur. Failure to adhere strictly to monitoring and evaluation of liver tests in the postmarketing setting, particularly when patients will be able to self-administer DAC, could lead to even more cases than would have been predicted based on findings in the clinical database. Other events of concern such as infections, skin reactions, and other immune-mediated events require prompt recognition, diagnosis, and appropriate treatment. Malignancies in the postmarketing setting may be detected late in absence of frequent contact with a healthcare provider as occurred in the clinical trials.

9. Advisory Committee Meeting

An advisory committee meeting is not planned.

10. Pediatrics

This application did not evaluate use in pediatrics. PERC has agreed to a waiver for pediatric studies based on safety and agreed with language in labeling to say that use of ZINBRYTA is not recommended in pediatric patients due to the safety risks.

11. Other Relevant Regulatory Issues

Please refer to the clinical efficacy review.

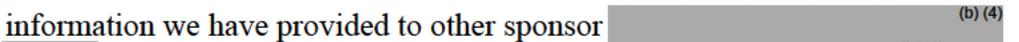
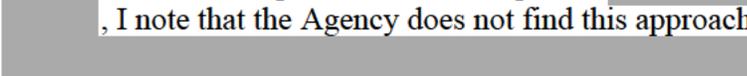
Drs. Villalba and Senior do not recommend approval based on safety concerns. Dr. Rosenberg recommend that the application either not be approved until the sponsor can address the safety issues and identify a strategy for patient selection, early detection and mitigation or be restricted to a subset of patients where the risk/benefit ratio is considered favorable. A recommendation regarding approvability can only be made based on a consideration of benefit and risk. If it is determined that DAC could be approved, I would recommend approving it for a restricted subset of the population.

12. Labeling

Prescribing Information

If DAC is approved, I have the following general labeling recommendations:

- DOSAGE AND ADMINISTRATION:
 1. Recommendations for laboratory monitoring, imitating daclizumab, and discontinuing daclizumab, will be necessary to mitigate the risks of hepatotoxicity.
- Safety information in the BOXED WARNING, CONTRAINDICATIONS, or WARNINGS AND PRECAUTIONS sections:
 1. I recommend a BOXED WARNING to describe the risk for potentially fatal hepatotoxicity and agree with recommendations to include immune-mediated events. These adverse reactions are serious, causally related to the use of DAC, and have implications for prescribing decisions and for patient management.
 2. Contraindication for pre-existing hepatic disease or hepatic impairment, a history of autoimmune hepatitis or other autoimmune condition involving liver, and a history of hypersensitivity to DAC.
 3. I recommend considering the following additional WARNINGS and PRECAUTIONS:
 - Skin Reactions
 - Acute Hypersensitivity
 - Multiorgan Hypersensitivity
 - Infections
 - Depression and Suicide
 - Breast Cancer (although based on uncertainty I think section 6 may be appropriate)
 - Lymphadenopathy
 4. I note that the sponsor proposed adding information (b) (4)

After discussion with Doran Fink in CBER on 5/26/16 and with reference to information we have provided to other sponsor (b) (4)
, I note that the Agency does not find this approach (b) (4)
 acceptable.

Other Labeling

A Medication Guide will be an important tool in educating patients and caregivers about the symptoms of hepatotoxicity, immune mediated reactions, and the other events identified in WARNINGS and PRECAUTIONS and to facilitate prompt recognition and treatment. In addition a Medication guide would provide information concerning the risks of DAC that could affect patients' decisions to use DAC.

13. Postmarketing Recommendations

Risk Evaluation and Management Strategies (REMS)

REMS are required risk management plans that use risk minimization strategies beyond the product labeling to ensure that the product's benefits outweigh its risks in the postmarket setting.

On March, 8, 2016, the REMS Oversight Committee (ROC) recommended a REMS with Elements to Assure Safe Use, including a registry, for daclizumab. The ROC was especially interested in whether patients with liver failure would be precluded from having a liver transplant due to autoimmune disease effects on the liver. If sufficient evidence of benefit supports approval, I agree that a REMS supporting strong product labeling will help ensure safe use of daclizumab.

Postmarketing Requirements (PMRs) and Commitments (PMCs)

I suggest a registry study of short term and long term safety if DAC is approved. Ideally this study would enroll every patient taking DAC, providing a known denominator that would be useful in calculating the incidence of specific adverse drug reactions including hepatotoxicity, autoimmune reactions, and malignancy once the drug is marketed. DNP has consulted with DEPI to plan for a PMR for a post-marketing observational study. The Sponsor has a planned observational, global drug observational study

(b) (4)
(b) (4)

I suggest a pregnancy registry and DNP has consulted with DEPI and DPMH to consider the language for such a PMR. The sponsor plans a pregnancy registry.

I recommend that the sponsor attempt to identify markers that could predict patients at risk for serious skin reactions or for drug-induced liver disease. In addition, Dr. Amy Rosenberg, in a review provided by email on March 4, 2016, has suggested the following PMRs:

- Correlate the extent of Treg depletion coupled with CD56hiNK enhancement in patients with autoimmune mediated AEs vs those not manifesting such responses and assess whether this could be used as a basis to develop an assay to predict autoimmune AEs
- Develop an in vitro assay of lymphocyte proliferation (spontaneous and induced) which could potentially provide a biomarker of autoimmunity. Given the

lymphoproliferation associated with loss of Treg function, this should be evaluated by the sponsor in patients who developed autoimmune AEs vs those that did not.

- Develop an RNA-seq analysis of lymphocytes to assess for a signature of autoimmunity that could be utilized to identify informative biomarkers.
- Assess *function* of Tregs following recovery of significant levels on cessation of DAC
- Assess earlier biomarkers of liver injury (see enclosed paper)
- Investigate the presence of autoantibodies to the spectrum of autoantigens observed in patients with mutations in IL-2RA and CTLA4 and their correlation to symptomatic autoimmune disease
- Consider approaches to mitigating severe autoimmunity that consider the likely mechanism of action, Treg depletion. Given the 6 month time to recovery of such cells following cessation of DAC, strategies that would increase Treg numbers or functionality, together with other immunosuppressive agents may more rapidly reverse and prevent tissue damage.

She also recommends the following additional studies and development of mitigation strategies:

- 1) The long term consequences of such treatment should be evaluated in Phase IV safety assessment.
- 2) Mitigation strategies that have been developed for checkpoint inhibition therapy should be employed in this setting, bearing in mind that some patients died despite implementation of such strategies. Models that evaluate these approaches as well as other approaches that may directly impact Treg numbers or functionality should be considered in informing mitigation strategies.

Recommended Comments to the Applicant

In any ongoing or future studies, the Sponsor should continue to monitor for adverse events of special interest as in the studies comprising this BLA. Laboratory monitoring should include glucose and calcium measurements. The Sponsor should consider how to facilitate compliance with laboratory monitoring and evaluation provided for in prescribing information.

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/s/

SALLY U YASUDA
05/26/2016

Clinical Review
 Lawrence Rodichok MD
 BLA 761029
 Zinbryta/Daclizumab High Yield Process/DAC HYP

CLINICAL REVIEW

Application Type	BLA
Application Number(s)	761029
Priority or Standard	Standard
Submit Date(s)	2/27/15
Received Date(s)	2/27/15
PDUFA Goal Date	5/27/15
Division/Office	DNP/ODE1
Reviewer Name(s)	Lawrence Rodichok MD
Review Completion Date	3/1/15
Established Name	Daclizumab
(Proposed) Trade Name	Zinbryta
Applicant	Biogen
Formulation(s)	150mg/mL liquid
Dosing Regimen	150 mg subcutaneously q4W
Applicant Proposed Indication(s)/Population(s)	Relapsing forms of Multiple Sclerosis
Recommendation on Regulatory Action	Approval
Recommended Indication(s)/Population(s) (if applicable)	Patients with relapsing forms of multiple sclerosis (b) (4)

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Glossary

AC	Advisory Committee
AE	Adverse event
ARR	Annualized relapse rate
BLA	Biologics license application
BPCA	Best Pharmaceuticals for Children Act
BRF	Benefit Risk Framework
CBER	Center for Biologics Evaluation and Research
CDER	Center for Drug Evaluation and Research
CDRH	Center for Devices and Radiological Health
CDTL	Cross-Discipline Team Leader
CFR	Code of Federal Regulations
CMC	Chemistry, manufacturing, and controls
CNS	Central Nervous System
CRF	Case report form
CRO	contract research organization
CRT	Clinical review template
CSR	clinical study report
CSS	Controlled Substance Staff
DAC	Daclizumab
DAC HYP	Daclizumab High Yield Process
DAE	Discontinuation due to an adverse event
DMC	Data monitoring committee
ECG	electrocardiogram
eCTD	Electronic common technical document
EDSS	Expanded Disability Status Scale
ETASU	Elements to assure safe use
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act of 2007
FDASIA	Food and Drug Administration Safety and Innovation Act
GCP	Good clinical practice
GRMP	Good review management practice
ICH	International Conference on Harmonization
IFN	Interferon
IM	Intramuscular
IND	Investigational New Drug
INEC	Independent Neurology evaluation committee

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ISE	Integrated summary of effectiveness
ISS	Integrated summary of safety
ITT	Intent to treat
IVRS	Interactive Voice Response System
MedDRA	Medical Dictionary for Regulatory Activities
mITT	Modified intent to treat
MS	Multiple Sclerosis
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Event
NDA	New drug application
NME	New molecular entity
NSAID	Non-steroidal anti-inflammatory drug
OCS	Office of Computational Science
OPQ	Office of Pharmaceutical Quality
OSE	Office of Surveillance and Epidemiology
OSI	Office of Scientific Investigation
OUS	Outside of the United States
PBO	Placebo
PBRER	Periodic Benefit-Risk Evaluation Report
PD	pharmacodynamics
PI	prescribing information
PK	Pharmacokinetics
PMC	Post-marketing commitment
PMR	Post-marketing requirement
PP	Per protocol
PPI	Patient package insert
PREA	Pediatric Research Equity Act
PRO	Patient reported outcome
PSUR	Periodic Safety Update report
Q4W	Every 4 Weeks
RCT	Randomized Controlled Trial
REMS	Risk evaluation and mitigation strategy
RMS	Relapsing Multiple Sclerosis
RRMS	Relapsing Remitting Multiple Sclerosis
SAE	Serious adverse event
SAP	Statistical analysis plan
SC	Subcutaneous
SGE	Special government employee
SOC	Standard of care
TEAE	Treatment emergent adverse event
US	United States
VFT	Visual Function Test

1 Executive Summary

1.1. Product Introduction

Daclizumab (DAC) is a humanized monoclonal antibody which binds to CD25, the α -subunit of the interleukin 2 (IL-2) receptor. Because CD25 expression on T cells is up-regulated after T cell activation daclizumab may reduce inflammation and CNS injury in patients with Multiple Sclerosis (MS). Daclizumab High Yield Process (DAC HYP) differs from previous versions of DAC in that it is manufactured using a new NS0-derived cell line and process. DAC HYP is considered a new molecular entity. The product is provided as a 150 mg/mL solution in a pre-filled syringe.

The proposed dose for the treatment of relapsing forms of Multiple Sclerosis (RMS) is 150 mg delivered subcutaneously (SC) in a single dose (b) (4)

1.2. Conclusions on the Substantial Evidence of Effectiveness

Data from a large randomized controlled study (205MS301 or Study 301) provides evidence that treatment with DAC HYP 150 mg SC q4W is statistically superior to treatment with interferon β 1a 40 μ g intramuscularly (IM) given weekly for the primary endpoint of reduction in the Annualized Relapse Rate (ARR) in patients with RMS. Data from a smaller study comparing two doses of DAC HYP, 150 mg and 300 mg q4W to treatment with placebo provides supporting evidence that DAC HYP reduces the ARR in RMS patients. The two studies constitute adequate substantial evidence of efficacy for an indication for the treatment of RMS. Relapses were associated with a mean change in EDSS of 1.5 points in the placebo group in Study 201 and in the Avonex group in Study 301. This change in EDSS likely translates to at least a temporary significant decline in level of function. This change was sustained for at least 12 weeks in approximately 25% of these subjects. Although evidence of a longer term reduction in disability is the most desirable benefit, the reduction in the disability associated with relapses is a relevant clinical benefit.

DAC HYP has not been shown to have a benefit on longer term disability that is better than that seen with Avonex. Although fewer subjects in Study 301 treated with DAC HYP 150 mg had progression of their disability, the difference compared to treatment with Avonex was not statistically significant for the pre-specified measure, the proportion of subjects with 12 week confirmed progression of disability. Avonex has been shown in a single previous study to reduce progression of disability when compared to placebo. Without a concurrent placebo arm in there is no assurance that Avonex had any effect on long term disability in Study 301. Although

not statistically significant using the pre-specified imputation method of assuming no progression if the tentative progression could not be confirmed, imputation of the rate of confirmation for the treatment group does result in a more significant advantage for DAC HYP 150 mg treatment. In study 201 the reduction in confirmed disability after one year of treatment was nominally significant but not included in the statistical analysis plan and therefore deemed not statistically significant. The treatment duration was too short and sample size too small to draw meaningful conclusions on this endpoint in Study 201. The absolute number of progressions is small. Nevertheless the relative reduction compared to placebo of 57% and 42% for the DAC HYP 150 mg and 300 mg respectively does provide some support for a reduction in disability with DAC HYP treatment. Alternate exploratory measures of function do not show a benefit from DAC HYP treatment. The final EDSS score and change from baseline in EDSS score at the end of treatment are within the interrater variability of the scale¹. The distance walked category did not change at the end of treatment. Therefore the evidence to support an effect of DAC HYP treatment on long term disability is limited.

Treatment with DAC HYP did reduce the various MRI measure of disease activity. These measures do not have an established relationship to patient function and therefore are supportive at best.

1.3. **Benefit-Risk Assessment**

Benefit-Risk Summary and Assessment

Multiple Sclerosis (MS) is a disorder of the Central Nervous System characterized by recurrent episodes of neurologic deficits in (relapses) scattered areas of the nervous system followed by a period of recovery that becomes less complete with each relapse. Over time the residual deficits from these episodes lead to an accumulation of disability. The onset of MS is typically between the ages of 20 and 40 years. MS is much more common in more northern latitudes including the US, Canada and parts of Europe where the prevalence is over 100 per 100,000 population¹. For relapsing forms of MS the median time to loss of independence is between 20 and 30 years from onset^{2,3}. Mortality is higher in patients with MS compared to the general population⁴.

Injectable β -interferons and glatiramer acetate reduce the relapse rate in MS and are relatively safe. The evidence that these products have an effect on long term disability is inconsistent. They are the most common initial therapies employed for the typical patient with RMS. These products require either subcutaneous or intramuscular injections. There are three approved oral therapies (fingolimod, dimethyl fumarate and teriflunomide) whose efficacy is comparable to the first line injectable therapies. Two monoclonal antibodies, natalizumab and alemtuzumab, are approved for RMS but because of serious safety concerns are usually limited to patients who have not responded adequately to other therapies.

In a large adequate and well-controlled trial DAC HYP has been shown to be superior to an approved β interferon in reducing the relapse rate in RMS. This benefit was supported by a smaller study in which two doses of DAC HYP were superior to placebo. A reduction in the frequency with which patients with MS are temporarily disabled by a relapse provides a relevant benefit. The evidence for a reduction in longer term disability are not statistically significant but do provide limited support for a relevant benefit beyond the reduction in relapses.

Treatment with DAC HYP is associated with more serious risks compared to the interferons and glatiramer acetate. The benefit of treatment with DAC HYP does not justify the risk for treatment naïve MS patient or for patients who have responded adequately to therapies with comparable efficacy and less serious risks.

¹ <http://www.msif.org/wp-content/uploads/2014/09/Atlas-of-MS.pdf>
http://www.who.int/mental_health/neurology/Atlas_MS_WEB.pdf

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Dimension	Evidence and Uncertainties	Conclusions and Reasons
<u>Analysis of Condition</u>	<ul style="list-style-type: none"> RMS is a condition associated with a risk of short term disability due to relapses and a risk of gradually increasing longer term disability due to incomplete recovery from relapses as well as from neurodegenerative changes. 	<p>MS is a condition that can result in a serious loss of function over the course of a relapse (months) as well as over the long term (years) course of the illness. The onset in early adulthood, most commonly in women of child-bearing potential, makes MS a seriously disabling illness.</p>
<u>Current Treatment Options</u>	<ul style="list-style-type: none"> There are multiple treatment options available. Current approved therapies reduce the relapse rate but have an inconsistent benefit on the accumulation of disability over 2 years or more 	<p>The β-interferons and glatiramer acetate are relatively safe but do not affect the relapse rate in all patients and have an inconsistent effect on long term disability. More recently approved therapies are generally associated with greater risk but offer an alternative to those who did not respond adequately to the interferons or glatiramer acetate.</p>
<u>Benefit</u>	<ul style="list-style-type: none"> The evidence for a reduction in the rate of relapses is consistent The evidence provided suggests that the reduction in long-term disability is approximately equivalent to that of currently available β-interferons 	<p>A reduction in the relapse rate this is superior to that of a β-interferon and a reduction in long term disability comparable to a β-interferon would justify the increased risk for those MS patients who need an alternative therapy.</p>

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Dimension	Evidence and Uncertainties	Conclusions and Reasons
<u>Risk</u>	<ul style="list-style-type: none"> • There is a significant risk of serious liver injury • There is a significant risk of autoimmune diseases typically seen with other monoclonal antibodies which target B and T cells 	See review of safety by Dr. Villalba
<u>Risk Management</u>	<ul style="list-style-type: none"> • It appears that surveillance for liver toxicity can be effective in identifying early hepatic injury • Early detection and discontinuation of treatment does not consistently reverse the liver toxicity 	See review of safety by Dr. Villalba

2 Therapeutic Context

2.1. Analysis of Condition

Multiple Sclerosis is a chronic disorder of the CNS characterized by recurrent episodes (relapses) of neurologic deficits that are due to one or more areas of acute injury to myelin, oligodendrocytes and to a lesser extent axons and neurons. Areas of acute inflammatory injury may involve subcortical white matter, brainstem, optic nerve and /or spinal cord. The diagnostic criteria for MS essentially require clinical and/or imaging evidence of a dissemination of these events “in space and time”⁵. Although early relapses may be followed by complete recovery, over time the recurrent relapses are associated with an accumulation of residual deficits and increasing disability⁶. Over time a slow progression of disability independent of the occurrence of relapses is seen in most patients with MS^{7,8}. Approximately 15% of patients with MS have a slowly progressive course from onset. Of those with a typical relapsing onset, approximately one-third will enter a slowly progressive phase with or without superimposed relapses⁹. Although disability can result from residual deficits following relapses¹⁰, relapses are probably not the dominant factor resulting in severe and permanent disability¹¹. Therefore a reduction in the relapse rate does not necessarily correlate with a significant reduction in long term disability. However the early frequency and severity of relapses and incomplete recovery from early relapses all tend to predict a more rapid progression of irreversible disability^{12,13}. Relapses are associated with a mean increase of 0.75 on the EDSS scale¹⁰. Most of the time the disability incurred at a relapse improves significantly within 2 to three months¹⁰. Increases on the EDSS that meet generally accepted criteria for confirmed progression of disability for 3 or 6 months are usually not sustained to one or two years¹⁴.

2.2. Analysis of Current Treatment Options

The currently approved therapies for RMS are shown in **Table 1** below. Available therapies reduce the relapse rate by 30 to 50%. While a reduction in the number of relapses is desirable it is unclear that this will result in a significant reduction in long term disability. Differences in methodology and the populations studied limit interpretation of the effect of these therapies on long-term disability. Several have shown a numeric reduction in some measure of disability that was confirmed 12 and/or 24 weeks after an initial significant increase in EDSS score. However, if a statistically significant reduction was seen in one trial, the result was usually not replicated in a second trial. There is insufficient evidence at this time to support the use of any of the MRI measures of disease activity as the primary criterion for the choice of therapy.

Because they were the earliest approved therapies and because there have been no major safety concerns, either a β -interferon or glatiramer acetate are often the initial choice for

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treatment for new onset typical RMS. Because the interferons share the same presumed mechanism of action and have similar efficacy, if the response is not adequate to one interferon then the choice of next therapy is usually not a different interferon and usually not glatiramer acetate. There are now several approved alternative therapies with efficacy at least comparable to the interferons and glatiramer acetate. The data available are not sufficient to conclude that the efficacy of any of the alternative therapies is superior to the older “first line” therapies. Each has somewhat unique benefits and risks. Unless there is strong evidence of superior efficacy and/or a notable lack of safety concerns, any new approved therapy will most likely be used for those who have not responded adequately to the interferons, glatiramer acetate and possibly one of the approved oral therapies.

Table 1: Approved treatment for Relapsing Forms of Multiple Sclerosis

FDA-Approved Treatments for Relapsing Forms of Multiple Sclerosis						
Approved Drug	Name	Sponsor	Approved	Dose	Frequency	Major Safety Concerns
Beta interferon 1b	Betaseron (Betaferon in the EU)	Bayer	1993	0.25 mg –(initial dose 0.0625 mg - gradually increase over 6 weeks)	SC qod	None
Beta interferon 1a	Avonex	Biogen Idec	1996	30 µg (may start at 7.5mg & increase by 7.5 µg weekly for 3 weeks)	IM q week	None
Glatiramer acetate	Copaxone	Teva	1996	20 mg/day	SQ qd	None
Mitoxanthrone	Novantrone	EMD Serono	2000	12mg/m ² IV over 5 to 15 min	IV q 3 mo	Cardiotoxicity
Beta interferon 1a	Rebif	EMD Serono Pfizer Inc.	2002	22µg or 44µg (start at 20% of target; increase over 4 weeks)	SQ tiw	None
Natalizumab	Tysabri	Elan	2004	300mg IV over 1 hour	every 4 weeks	PML
Beta interferon 1b	Extavia	Novartis	2009 (1993)	0.25 mg –(initial dose 0.0625 mg - gradually increase over 6 weeks)	SQ qod	None
Fingolimod	Gilenya	Novartis	2010	0.5 mg	orally once daily	First dose bradycardia CI for recent MI, unstable angina, TIA,CHF Macular edema Impaired PFTs Fetal risk
Teriflunomide	Aubagio	Sanofi	2012	7 mg or 14 mg	orally once daily	Black box warning for hepatotoxicity and teratogenicity; additional concerns for WBC decrease, renal failure, skin reactions; peripheral neuropathy
Dimethyl fumarate	Tecfidera	Biogen-Idec	2013	120 mg for 7 days, then 240 mg	twice daily	Lymphopenia

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FDA-Approved Treatments for Relapsing Forms of Multiple Sclerosis						
Approved Drug	Name	Sponsor	Approved	Dose	Frequency	Major Safety Concerns
PEGylated interferon β	Plegridy	Biogen	2014		Q2 weeks	None
Alemtuzumab	Lemtrada	Genzyme	2015	1 st course: 12 mg/dy X5 2 nd course: 12 mg/dy X3	2 courses 12 months apart	Black box warning for serious/fatal autoimmune conditions including thrombocytopenia and anti-glomerular basement membrane disease; serious and life-threatening infusion reactions; special facilities required for infusion; increased risk of malignancies; REMS

3 Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

Daclizumab High Yield Process (DAC HYP) is considered a new molecular entity. Daclizumab manufactured using a different process was approved in the United States on December 10, 1997 under BLA 103749 for the prophylaxis of acute organ rejection in patients receiving renal transplants. Zenapax® was withdrawn from the market in the European Union effective on January 1, 2009 and from the US market in September 2009. The sponsor indicated that the reason for withdrawal was commercial. The European Medicines Agency confirmed that the withdrawal was not for safety concerns. The label included a black box warning for use only by physicians experienced in immunosuppressive therapy and management of organ transplant patients. Zenapax® was contraindicated in patients with known hypersensitivity to daclizumab.

3.2. Summary of Presubmission/Submission Regulatory Activity

IND 012120 for the use of Daclizumab High Yield Process (DAC HYP) for the treatment of multiple sclerosis was submitted by PDL BioPharma, Inc on December 3, 2004. The first clinical trial was allowed to proceed on January 5, 2005. The IND was never on clinical HOLD.

The sponsor was changed to Facet Biotech Corporation on December 19, 2008 and to Abbott Biotherapeutics on January 11, 2011. The parent company, Abbott Laboratory changed its name to AbbVie on August 2, 2012. On May 12, 2015 sponsorship was transferred from AbbVie to Biogen, Incorporated.

Fast Track designation was denied on April 1, 2011.

The Pediatric Plan includes a waiver for the study of patients (b) (4)
(b) (4) On November 26, 2014 an agreement letter was issued
(b) (4)

The End of Phase 2 meeting was held on July 24, 2008. Issues of note at that meeting were the following:

1. There was a concern for the potential behavioral effects of the finding of microglial aggregates in the CNS of monkeys. (b) (4)
(b) (4)

2. FDA indicated that demonstration of a statistically significant effect on the primary endpoint in one study at 1 year and in a second study at 2 years with at least 2 years of controlled safety data from each study would potentially support registration of daclizumab.

A special protocol assessment for Study 301 was requested on August 25, 2009.

A No Agreement letter was issued on October 9, 2009 with the following comments to sponsor that are relevant to the current application:

1. It was recommended that disability progression be specified as the first key secondary endpoint. (This endpoint is the second of the key secondary endpoints in the protocol for which an SPA agreement was reached).

An SPA Agreement letter was issued on May 28, 2010

A No Agreement letter to proposed modifications to the SAP was issued on April 28, 2014.

(b) (4)

(b) (4)

3.3. Foreign Regulatory Actions and Marketing History

Daclizumab High Yield Process is not approved outside the United States.

4 Significant Issues from Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety

4.1. Office of Scientific Investigations (OSI)

The following sites were inspected:

Table 2: Reviewer table: OSI site audits and final classification.

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Site number/Location/PI	Protocol/#subjects	Final classification
604/Poland/ Selmaj	Study 301/54	NAI
659/Czech Republic/ Dufek	Study 301/23	NAI
670/Serbia/ Nadj	Study 301/41	VAI
611/Poland/ Zielinski	Study 301/40	NAI
453/Italy/ Patti	Study 301/40	VAI
459/Italy/ Centonze	Study 301/14	VAI

NAI: No deviations; no action indicated

VAI: Deviations from regulations; voluntary action indicated

Reviewer Comment: The deviations that were found were infrequent and were considered unlikely to have had any impact on key efficacy or safety results. Examples of minor deviations were visits conducted outside of the protocol-defined window and isolated examples of concomitant medications not recorded.

4.2. **Product Quality**

See the review by Dr. Chen Sun

4.3. **Clinical Microbiology**

See the review by Dr. Bo Chi

4.4. **Nonclinical Pharmacology/Toxicology**

See the review by Dr. David Carbone

4.5. **Clinical Pharmacology**

See the review by Dr. Ta-Chen Wu

4.5.1. **Mechanism of Action**

See the review by Dr. Ta-Chen Wu

4.5.2. **Pharmacodynamics**

See the review by Dr. Ta-Chen Wu

4.5.3. **Pharmacokinetics**

See the review by Dr. Ta-Chen Wu

4.6. **Devices and Companion Diagnostic Issues**

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The product is supplied as a prefilled syringe.

4.7. **Consumer Study Reviews**

Not applicable

5 Sources of Clinical Data and Review Strategy

5.1. **Table of Clinical Studies**

APPEARS THIS WAY ON ORIGINAL



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Table 3: Listing of Clinical Trials Relevant to this BLA

Trial Identity	Trial Design	Regimen/ schedule/ route	Primary Study Endpoint	Treatment Duration/ Follow Up	No. of patients enrolled	Study Population	No. of Centers and Countries
<i>Controlled Studies to Support Efficacy and Safety</i>							
Study 201 (SELECT)	RCT; 2 doses vs. placebo	150 mg or 300 mg q4W	ARR	52 weeks	621	Relapsing forms of MS	78 sites in 9 countries – all OUS
Study 301	RCT; 1 dose vs. IFN β 1a	150mg SC q4W vs 30 µg IM qW	ARR	96 weeks	1841	Relapsing forms of MS	245 sites in 28 countries
<i>Studies to Support Safety</i>							
205MS 202	RCT extension of Study 201; 2 doses of DAC HYP; initial placebo X4 doses for 2 cohorts	150 mg or 300 mg q4W	Safety and immunogenicity	52 weeks	517	Relapsing forms of MS; Study 201 completers	73 sites in 8 countries
205MS 203	Open label extension of 202	150 mg q4W	Safety	Up to 6.5 years	410*	Relapsing forms of MS	Same as 201
205MS302	Open label extension of 301	150 mg q4W; washout X 20 weeks; 150 mg q4W	Immunogenicity and PK		133*	Relapsing forms of MS	Same as 301
205MS303	Open label extension of 301	150 mg q4W	Safety	Up to 144 weeks	1033*	Relapsing forms of MS	Same as 301
<i>Other studies pertinent to the review of efficacy or safety (e.g., clinical pharmacological studies)</i>							
DAC-1012	RCT; 2 doses vs. placebo	1 mg/kg; 2 mg/kg; PBO	Total Gd- enhancing lesions	24 weeks	230	Relapsing forms of MS	51 sites in 5 countries including the US

RCT: Randomized, controlled trial; PBO: placebo

*: at the time of submission

5.2. Review Strategy

This review is focused primarily on the results of Study 301 because it is the only study submitted in which treatment duration was for at least 2 years and the key efficacy endpoints are assessed after two years of treatment. Study 201 is a smaller study (approximately 200 subjects per treatment arm) in which treatment was for one year. The Division of Neurology Products does not typically consider one year an adequate period to assess the effect on the ARR and on progression of disability and to assess the stability of any benefit over time. Study 201 was intended in part to assess any difference in efficacy and safety between 150 mg and 300 mg SC q4W compared to placebo.

Reviewer Comment: At the End of Phase 2 meeting "FDA indicated that demonstration of a statistically significant effect on the primary endpoint in one study at 1 year and in a second study at 2 years with at least 2 years of controlled safety data from each study would potentially support registration of daclizumab". See Section 3.2.

6 Review of Relevant Individual Trials Used to Support Efficacy

6.1. Study 301 - Multicenter, Double-blind, Randomized, Parallel-group. Monotherapy, Active-control Study to determine the Efficacy and Safety of Daclizumab High Yield process (DAC HYP) versus Avonex (Interferon β -1a) in Patients with Relapsing-Remitting Multiple Sclerosis

Study 301 is the primary source of data to support a claim of β efficacy.

6.1.1. Study Design

Overview and Objective

The primary objective of this study was to demonstrate the efficacy of DAC HYP 150 mg SC q4W in patients with RRMS by showing superiority to the active concurrent comparator Avonex (interferon β 1a) in reducing the annual relapse rate after two years of treatment.

Trial Design

Study 301 utilized a prospective randomized double-blind double-dummy parallel group design in which all subjects received a subcutaneous injection of either DAC HYP 150 mg q4W or a weekly intramuscular injection of 30 μ g of Avonex for a minimum of 96 weeks. All subjects received matching injections of intramuscular or subcutaneous placebo.

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The use of a double-dummy design is important for blinding since Avonex and DAC HYP are given with different timing and routes of administration. The choice of attempting to demonstrate the superiority of DAC HYP to a well-established interferon is important in the interpretation of the risk benefit comparison since Avonex has been shown to benefit both the annualized relapse rate and, in a single trial, a reduction in the progression of disability. The DAC HYP dose of 150 mg SC q4W was selected based on the results of Study 201 (SELECT) in which doses of 150 mg and 300 mg q4W were compared to placebo (see 6.2) and study DAC-1012 (“CHOICE”) in which doses of 1 mg/kg and 2 mg/kg were studied.

Study 301 was conducted in 28 countries at a total of 246 sites including 49 sites in the United States and 9 in Canada. Sites were in Eastern and Western Europe, Scandinavia, Asia and South America.

Reviewer Comment: The inclusion of sites from a wide range of geographic locations is reasonable. Any differences in treatment of MS, particularly the algorithm for the use of “disease-modifying” treatments such as DAC HYP, in different countries have not been systematically studied. Nevertheless there have been no indications that there are major differences in the treatment of MS between the regions from which sites were selected.

The date of first subject treated was May 11, 2010 and the Last Patient Last Treatment Period Visit date was March 5, 2014. The last follow-up assessment occurred on July 28, 2014. Database lock was September 16, 2014.

The study objective was to show superiority to an active comparator, Avonex. Avonex has been shown to reduce the annual exacerbation rate compared to placebo from 0.82 to 0.67 (relative reduction of 18%) at 2 years, to reduce the proportion with progression of disability from 35% to 22% (relative reduction of 37%) at 2 years, as well as to reduce the occurrence of various MRI measures of disease activity².

The key eligibility criteria for this trial allowed inclusion of patients who fulfilled the generally accepted McDonald criteria¹⁵ for relapsing MS as revised in 2005¹⁶. In addition, evidence of recent disease activity was required. Recent activity could be demonstrated by recent clinical relapses and/or evidence of new lesions on MRI scan. Those with a very recent relapse, i.e. within 50 days were excluded. Patients with any progressive form of MS including secondary progressive forms were excluded. The baseline EDSS score had to be 5.0 or below, i.e. patients had to be able to walk at least 200 meters without aid or rest but some of their activities of daily living may have been impaired. Patients being treated with Avonex were not excluded.

² http://www.accessdata.fda.gov/drugsatfda_docs/label/2015/103628s5258lbl.pdf

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Patients with a history of prior treatment with most other “disease-modifying” or immunosuppressive therapies for MS were excluded if the treatment had occurred within a specified interval varying from as long as one year (e.g. natalizumab) to as short as 30 days (glatiramer acetate and IV or oral corticosteroids) prior to randomization.

Reviewer Comment: The eligibility criteria are reasonable and comparable to those for studies of the products currently approved for the treatment of RMS. The criteria are expected to yield a study population of subjects who are either treatment naïve or who continue to have relapses despite previous “disease modifying” therapy. Such a population would be typical of a population being treated in clinical practice in the US and OUS. The complete eligibility criteria are in Appendix 13.3.

Prospective subjects were to be screened for eligibility no more than 4 weeks prior to the baseline visit at which the reference EDSS score was to be recorded.

The planned duration of treatment was a minimum of 96 weeks but no greater than 140 weeks. Subjects who completed the trial were eligible for continued treatment in an open label extension study (205MS302). Subjects who did not enter the extension study were to have follow-up visits at 8, 12, 16, and 24 weeks after the last dose of study treatment. These four visits could be used to confirm a tentative progression of disability by EDSS.

Reviewer Comment: The duration of treatment for approximately 2 years is comparable to that in most recent studies of treatments approved for RMS. It allows an adequate period to assess the effect on the ARR and on progression of disability and to assess the stability of any benefit over time.

Those randomized to DAC HYP were treated with 150 mg SC q4W. This dose was selected based on the results of Study 201 which was interpreted by the sponsor to show no additional benefit in the 300mg SC every 4 week group. The dose of Avonex, 30 µg IM every week, was the approved dose for treatment of RMS. Avonex was administered by subjects or another caregiver while DAC HYP was administered in a clinic setting.

Reviewer Comment: Doses of an earlier formulation of daclizumab lower than 150 mg q4W, i.e. 1 mg/kg SC q4W in Study DAC-1012, were expected to be less effective than the 150mg dose. Study DAC-1012 relied primarily on surrogate endpoints and was studied in subjects on concurrent interferon β therapy. Nevertheless the dose of daclizumab selected for this Study 301 is reasonable.

A dose of study medication could be delayed or omitted for a fever, evidence of infection, skin reaction, reduction in white blood cell, lymphocyte or platelet count, or elevated liver function studies. The protocol called for resumption of dosing or permanent discontinuation of

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treatment based on criteria for resolution of the problem. Compliance with Avonex administration was “monitored and recorded in the subject’s CRF by site staff”.

Concurrent and rescue medications

For the first 24 weeks of the trial subjects were instructed to take an anti-inflammatory drug, most commonly acetaminophen or ibuprofen, prior to each Avonex/Avonex placebo injection and during the 24 hours after the injection. The use of these drugs after 24 weeks was at the discretion of the investigator. These drugs were permitted if necessary to treat flu-like symptoms if they occurred beyond 24 hours after the injection.

The use of anti-inflammatory agents beyond the first 24 weeks could be a measure of the frequency of administration-related adverse events. Whether subjects did or did not use these medications prior to and after administration of investigational product was recorded in the CRF throughout the trial. See page 61 of this review.

Subjects could choose to continue the investigational treatment despite the occurrence of a relapse (repeat consent was required). Thus some subjects may have experienced more than one relapse during the trial. Those who completed the protocol-defined treatment were eligible for the long term open label trial (205MS302). Those who discontinued treatment prematurely (prior to week 140) were expected to attend a modified schedule of follow-up assessments 8, 12, 16 and 24 weeks after the end of treatment (as for those who completed the planned treatment but who chose not to enter the extension study these visits could be used to confirm a tentative progression of disability by EDSS).

Concomitant treatment with alternative therapies for MS were not permitted and a reason for discontinuation. Treatment for an acute relapse with systemic corticosteroids was permitted but subjects could refuse this treatment for a relapse. Symptomatic treatment such as dalfampridine could not be initiated during the trial although a stable dose of such a treatment was allowed at entry.

Study specific reasons for withdrawal or discontinuation

Subjects were discontinued if treatment with a prohibited medication was required or if there was a hypersensitivity or suspected allergic reaction to the study treatment. Subjects were also discontinued if elevated liver function studies or depressed blood cell counts met specific criteria (protocol Section 11.2.1). There were no other study-specific reasons for withdrawal. All subjects who withdrew from the study or who discontinued treatment before week 140 were to be asked to continue in the study for a modified schedule of efficacy and safety assessments at 8, 12, 16 and 24 weeks after discontinuing treatment.

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Randomization

Randomization was 1:1 using an interactive voice response system. Stratification was by site and prior treatment with a β interferon.

Blinding

Efforts to maintain blinding included the use of the double-dummy design. A placebo matching the appearance of both DAC HYP and Avonex were used. Most patients being treated with Avonex experience a local injection reaction and/or flu-like symptoms within hours to days after the injection. Subjects were instructed by the treating neurologist and/or treating technician to conceal the injection site(s) from the examining neurologist/technician at the time of an EDSS or relapse assessment. The treating neurologist and/or technician were to assess injection sites for evidence of a local reaction. The treating neurologist and/or technician were responsible for medical management, reporting of adverse events and were to review laboratory results. Since flu-like symptoms and fever are likely to occur with Avonex and DAC HYP infusions as well, all subjects were treated with anti-inflammatory agents within 24 hours prior to and after each injection. After 24 weeks the anti-inflammatory drugs could be discontinued or continued at the discretion of the investigator.

The treating nurse was responsible for informing the treating neurologist if the subject met the endpoint criteria for sustained progression of disability. The treating neurologist made the decision as to whether symptoms of a potential relapse reported by a subject should be further evaluated by the examining neurologist or dismissed as not related to a relapse. The clinical assessments that were key to the determination of whether a relapse had occurred, i.e. the presence of an “objective” neurologic deficit, were performed by an “examining neurologist” or “examining technician” who were to remain blinded to treatment assignment, adverse events and laboratory results. Similarly, since the EDSS is susceptible to bias¹⁷, this key measure of progression of disability was performed by the examining neurologist and/or technician who were not to have access to any clinical or laboratory data. A blinded independent neurology evaluation committee (INEC) made the final determination as to whether a relapse had occurred based on the data transmitted by the treating and examining neurologist/technician.

To assess the success of these blinding procedures the sponsor was asked to assess for any bias in the selection of events for further evaluation by the examining neurologist and/or technician and in the determination of relapses by the INEC.

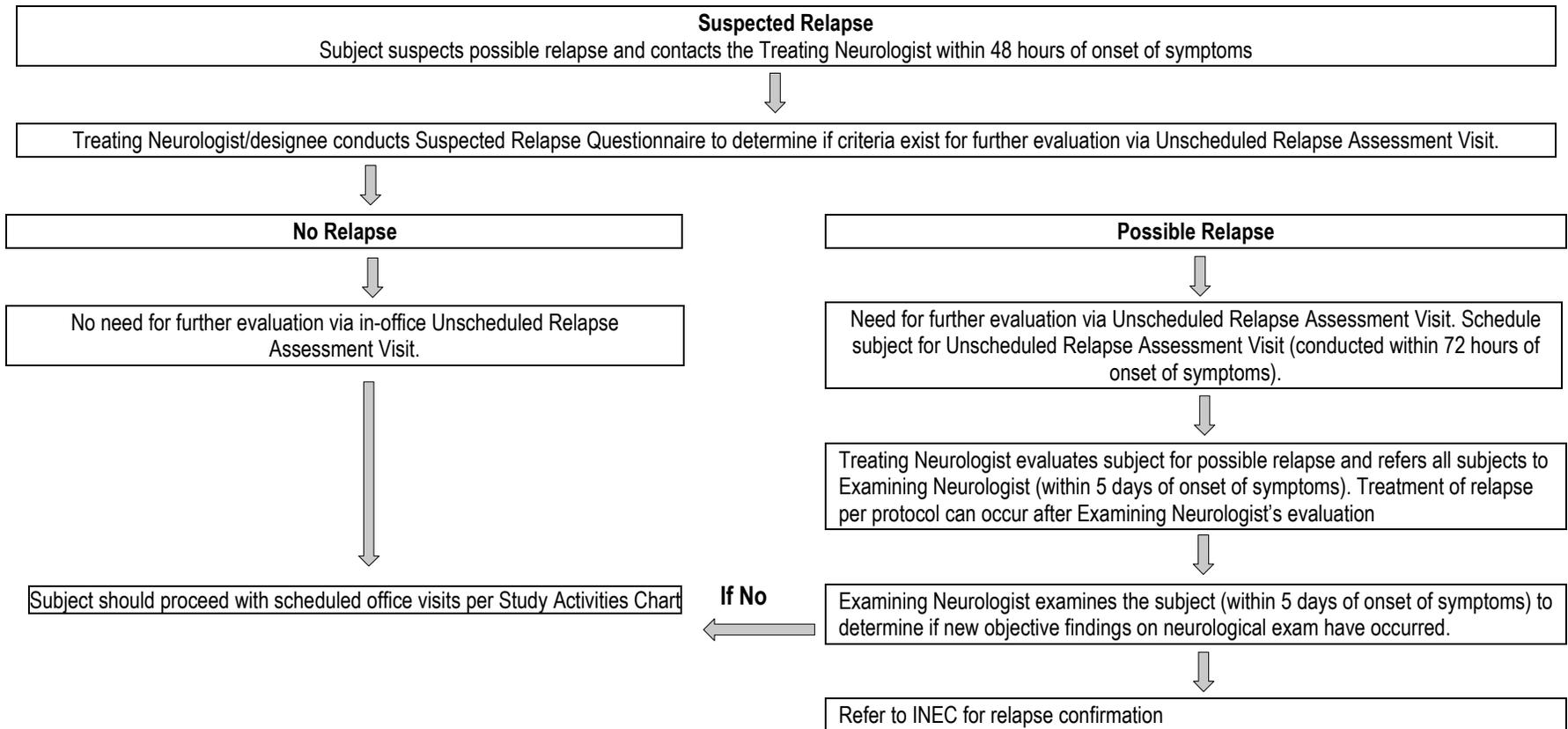
Assessments

The key assessments for Study 301 are those shaded in the Figure 1 below. An EDSS assessment was performed at scheduled visits every 12 weeks and at any unscheduled visit, typically for a possible relapse. An MRI scan was done at week 24 and 96. The process for evaluation of a possible relapse is summarized in Figure 2 below. Treatment and assessments could continue up to week 140.

Figure 1: Reviewer Figure: Study 301 Key Assessments

	Screening	Baseline	Study Week																									
			0	4	8	12	16	20	24	28	32	36	40	44	48	52	56	60	64	68	72	76	80	84	88	92	96	
Hematology																												
Chemistry																												
EDSS																												
MRI																												
DAC HYP IvI																												
DAC HYP adm																												

Figure 2: Reviewer Figure: Relapse Assessment Process



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Identification of a relapse

Subjects who suspected that they were experiencing a relapse were expected to contact the treating neurologist within 48 hours of symptom onset. A standardized “Suspected Relapse Questionnaire” was to be completed to determine the necessity of an Unscheduled Relapse Assessment Visit (Protocol section 14.3.8). If required, the subject was to then be evaluated in person by the Treating Neurologist as soon as possible and within no more than 72 hours of the onset of the potential relapse. The site operation manual states that the “Suspected MS Relapse Questionnaire – INEC Alert Form” should only be completed if the suspected MS Relapse case is sent to INEC for review”.

Reviewer Comment: The 74-day letter included an information request for the data from these forms in order to document the details of this process and in particular to allow an assessment of whether there was any bias in the determination of which subjects would be assessed in person for a possible relapse.

A relapse was defined as any new or recurrent neurologic symptoms that correlated 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 was included in the assessments by the examining neurologist/technician if the event was referred by the treating neurologist.

Reviewer Comment: At the pre-BLA meeting the sponsor was asked to “describe the detailed sequence used for identification of relapses from the initial subject report to confirmation by the Independent Neurology Evaluation Committee (INEC)”. The sponsor was asked to include the time that the symptoms were first reported by the subject, the time of first assessment by the treating neurologist, the time of examination by the examining neurologist and the time the data was sent and reviewed by the INEC. These are all provided in the RL and ES datasets. The sponsor was asked to provide analyses that would assess any potential bias in the process of evaluating relapses – this was provided in submission e0030. The sponsor was asked to provide analyses of relapses as reported by subjects, as determined by the results at the investigative site in addition to the primary analysis as determined by the INEC. These are provided in the Study 301 CSR. All INEC reviews were to be based on subject examination records from the treating and examining neurologist but without knowledge of the subject’s treatment assignment and without MRI data.

Disability

An EDSS assessment was to be completed every 12 weeks and at unscheduled visits. The EDSS was to be completed as part of any potential relapse when the treating neurologist determined that a patient report of new symptoms met the protocol definition of a relapse. All EDSS assessments were to be completed an “examining neurologist” who was not involved in the

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care of the subjects and was unaware of other clinical results such as adverse event reports and laboratory results. The (b) (4) score sheet and definitions version 12.05 were used to determine the total EDSS score.

Study Endpoints

The primary efficacy endpoint was the annualized relapse rate (ARR). This has been a generally acceptable primary endpoint for approval of treatments for relapsing MS. A reduction in the ARR may or may not correlate with long term disability. An assessment of the severity of the relapses may be important since the protocol for Study 301 did not include a required incremental increase in neurologic deficit to qualify as a relapse. Data to assess the severity of the relapses included in the primary analysis was collected.

Reviewer Comment: The definition of a relapse only required that there be a new “objective” neurologic deficit. The increase in EDSS score as assessed by the examining neurologist should give some indication of the severity of the relapses at onset.

The key secondary endpoints in their order in the statistical sequential hierarchy were:

1. The number of new or newly-enlarging T2 hyper-intense lesions on MRI over 96 weeks
2. The proportion of subject with progression of disability as defined in the protocol and sustained for 12 weeks
3. The proportion of subjects who were free of any relapse
4. The proportion of subjects with a ≥ 7.5 point worsening from baseline in the Multiple Sclerosis Impact Scale physical score at 96 weeks.

Assessment of safety including adverse events, vital signs, laboratory studies and the assessment of suicidality were included and will be addressed in detail by the safety reviewer.

Statistical Analysis Plan

The study was conducted under an SPA agreement (Initial agreement 30 October 2011; Final SAP Version: 23 May 2014).

Sample Size calculation

The sample size was based on the assumption of an ARR of 0.27 in the IFN β -1a group and a reduction by 24% in the DAC HYP group over an average of 2.4 years of follow-up. A drop-out rate of 21% was assumed for the two year study. Approximately 900 subjects per treatment arm would yield 90% power to detect the projected treatment effect. The assumptions are based on the use of a negative binomial regression model with a 5% type one error rate.

Reviewer Comment: In the trial the actual adjusted ARR in the Avonex group was 0.393.

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There was no interim analysis.

Subjects were randomized 1:1 stratified by site using permuted blocks (CSR section 9.4.3).

The primary endpoint, the annualized relapse rate, was to be determined for a modified the intent to treat population, defined as all randomized subjects who received at least one dose of any study medication. The primary endpoint analysis was to include only protocol-defined relapses up to the end of treatment period visit that had been confirmed by the INEC. Relapses that occurred after the start of an alternative treatment for MS were excluded and such a subject's time on study was censored at the day of start of the alternative treatment. A relapse with an onset that occurred ≤ 29 days after another INEC-confirmed relapse was to be considered the same relapse. The primary method of calculating the ARR used a negative binomial regression model. The model was adjusted for baseline relapse rate (the number of relapses in the three years prior to study entry divided by 3), history of prior interferon treatment (a stratification factor), baseline EDSS (2.5 or less versus more than 2.5) and age 35 or less versus more than 35.

The "unadjusted relapse rate" rate was to be calculated as the total number of relapses in the treatment group divided by the number of days in the study at the End of Treatment Period Visit or at the time of censoring for the group. This ratio is multiplied by 365.25. For those who completed the study the End of Treatment Period Visit was the Last Scheduled Treatment Period Visit. For those who discontinued treatment prematurely, the End of Treatment Period Visit was either the Last Scheduled Treatment Period visit or the date of last follow-up visit that occurred prior to 180 days after the last dose of study medication.

Reviewer Comment: A "tertiary endpoint" was the annualized relapse rate for severe or serious relapses (SAP Section 6.4.1.3). This calculation was performed for all "severe or serious relapses" regardless of whether INEC-confirmed. A serious relapse and a severe relapse were not defined in the SAP, protocol or clinical study report. In response to an information request the sponsor indicated (submission e0015) that a "serious" relapse was one that was reported as a serious adverse event. A "severe" relapse was one whose intensity was rated as severe.

The primary and secondary endpoints were to be tested at the 0.05 significance level with a closed testing procedure for the secondary endpoints in the order specified, i.e. **1)** The number of new or newly enlarging T2 hyper-intense lesions on MRI over 96 weeks **2)** The proportion of subject with progression of disability as defined in the protocol sustained for 12 weeks **3)** The proportion of subjects who were free of any relapse **4)** The proportion of subjects with a ≥ 7.5 point worsening from baseline in the Multiple Sclerosis Impact Scale physical score at 96 weeks.

Progression of disability was defined as an increase on the EDSS of 1 point or more for subjects

with a baseline EDSS of 1 or more or an increase of 1.5 points or more for those with a baseline EDSS of 0. Confirmation of the increase was required at a visit that occurred 74 days (minimum window for 12 weeks) or more later. The onset of a period of progression could occur at a relapse but confirmation could not occur at a visit at which a relapse was occurring. If the first qualifying confirmation visit occurred during a relapse then the confirmation could occur at the next qualifying visit. For subjects with a missing baseline EDSS score, the EDSS score at screening was to be used. EDSS scores from study 205MS303 up to week 12 or from the planned follow-up visits for those who did not enroll in the extension study could be used for confirmation. Confirmation could occur after the start of alternative MS treatment. The start of the progression would be the date of the EDSS score at the start of the progression period. Subjects who did not meet the criteria for progression of disability were to be censored at the last EDSS assessment collected on treatment or prior to the End of Treatment Period visit or prior to the start of alternative MS treatment. The calculation of the time to onset of confirmed disability progression used the Kaplan Meier model. Calculation of the proportion of subjects who met the criteria used the Cox proportional hazards model adjusted for baseline EDSS, prior use of interferon β and baseline age group. The following sensitivity analyses were planned:

- For those who have a tentative progression but then drop out of the study, multiple imputation approach would be used that will be based on a model for that treatment group.
- Progression not counted if the tentative progression occurred during a relapse
- Assume that all tentative progressions without a confirmatory EDSS >74 days after the tentative progression are confirmed.

Reviewer Comment: The sponsor's calculation of this endpoint included progressions that started on or prior to the End of Treatment Visit. Those who did not meet the criteria for progression of disability were censored at the last EDSS assessment prior to the End of Treatment visit. If this endpoint was limited to onset of disability at or prior to the Week 96 visit the result would have been approximately the same.

Proportion of subjects who were relapse-free

The calculation of the proportion of subjects who are relapse free is based on the inverse of the cumulative probability of a relapse from the Kaplan-Meier calculation of time to first relapse.

All efficacy endpoint analyses were to include as covariates the baseline covariates and the stratification variable, i.e. prior interferon use.

Once the last enrolled subject completed the week 96 visit, all ongoing subjects were to complete an End of Treatment Period visit. Thus it was anticipated that the actual duration of treatment for all participating subjects would vary from a minimum of 18 months to a

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maximum of 140 weeks.

Study completion was defined as having continued into study 205MS303 or at least 180 days of follow-up after the Last Dosing Date.

The reasons for premature withdrawal or discontinuation from the study and/or study treatment were reclassified prior to database lock based on a review of additional textual information provided in the CRF. The new classifications were to include: MS/Lack of Efficacy, Non-compliance, Site closure, other and consent withdrawn.

Time on treatment was based on the number of days from the first dosing data to the Last Dosing Date. The time of exposure to study treatment was calculated from the date of the first dose of active drug or placebo to 180 days after the Last Dosing Date.

Pre-specified subgroup analyses included analyses by baseline EDSS score, number of relapses prior to randomization, prior treatment with interferon, prior immunomodulatory treatment and by region.

Study Committees

An advisory committee consisting of Biogen Idec employees and independent investigators provided scientific direction and oversight of study conduct, provided assessment of subject eligibility when and if there was a question, and monitored recruitment. A recognized expert in multiple sclerosis, (b) (4) was the Advisory Committee chairperson.

A Data and Safety Monitoring Committee (DSMB) provided safety monitoring for the trial. Members of the DSMB were not allowed to participate as investigators in the study. A non-voting independent statistician was unblinded to the subjects' treatment assignments and prepared reports for the closed sessions. These reports included partially unblinded data, i.e., data summarized by group but not labeled as to the actual group. The Sponsor did not have access to the closed reports. At each scheduled meeting, after reviewing the data, the DSMB made a recommendation to continue, stop, or modify the study based on any safety findings. Because the DSMB did receive reports of relapses when they were reported as adverse events, members could become aware of a difference in risk vs. benefit between the two arms of the trial. Open but not closed sessions included sponsor representatives.

An Independent Neurology Evaluation Committee (INEC) made the determination as to whether a subject had experienced an MS relapse as defined by the protocol. The INEC included 5 members, all of whom were neurologists with expertise in MS. INEC members were not permitted to be investigators in the trial. At any one time, there were 3 voting INEC members. Members were assigned on a rotating basis so that different combinations of members participated at a given time.

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MRI scans were assessed by a group of approximately 26 readers at (b) (4) an independent vendor. A detailed charter of procedures has been provided in Appendix 16-1-10. In general the interrater variability was low with the exception of the results for gadolinium-enhancing lesion volume where the mean Normalized Total absolute difference (NTAD), which was a comparison of the reader variability to that of a group of “experts”, was 13%. Intra-rater variability was low for all assessments.

EDSS scale training and certification was required of all investigators within the 12 months prior to the study start date. Training and Certification were provided (b) (4)

Protocol Amendments

The original version of the protocol was final on 9 November, 2009

Version 2, 27 May 2011 included the following key revisions:

- Increased monitoring of liver function tests and the addition of revised criteria for discontinuation of subjects for LFT abnormalities
- Criteria for withholding a dose for persistent fever or infection
- Additional guidance to investigators on the evaluation and management of cutaneous events including suspension of dosing
- Increase in sample size from 750 to 900 per treatment arm (Based on new literature reports the expected ARR in the placebo arm was revised from 0.30 to 0.27).

Version 3, 10 March 2012 was revised as follows:

- Prohibit concomitant treatment with hepatotoxic drugs
- Provide the results of monthly liver function studies to treating neurologist prior to administration of study treatment

Version 4, 29 April 2013 included the following revisions

- The ranking of the secondary endpoint sequential hierarchy was changed. The number of new or newly enlarging T2 hyperintensities remained first, the proportion of subjects with sustained disability progression was moved to the second endpoint, the proportion relapse free became the third and the proportion with a ≥ 7.5 point worsening from baseline on the MSIS-29 physical score at 96 weeks was added as the fourth. The change in the Multiple Sclerosis Functional Composite score was removed (had been second) and the change in the Multiple Sclerosis Impact Scale-29 physical score was removed (had been third)

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Reviewer Comment: At the time of the above amendment all 1841 subjects had been enrolled and 1522 subjects were still participating in the trial (see response to request for additional information in e0058)

Data Quality and Integrity: Sponsor's Assurance

Site initiation visits were to be conducted prior to screening any patients. Initiation visits included protocol training. A Contract Research Organization (CRO) was responsible for site initiation visits, monitoring for data integrity and management of SAE reporting to the sponsor. An IVRS system was used for randomization. Study data was captured using an electronic CRF. The charter for the DSMB is included in the Statistical Analysis Plan document.

6.1.2. Study Results

Compliance with Good Clinical Practices

The sponsor has provided attestations in the final Clinical Study Report (CSR) that the study was conducted in accordance with 21CFR Parts 50, 54, 56 and 312 Subpart D. The study was also conducted in accordance with European Union (EU) Guidelines 2001/20 and Good Clinical Practice guideline 2005/28 as well as International Conference on Harmonization E6. Investigators obtained approval of the protocol and amendments from Institutional Review Boards (IRB) or Ethics committees (EC) in the EU and United States (US). A listing of the IRBs and ECs is provided in a CSR appendix. The sponsor asserts that the study was in compliance with the ethical principles in the Declaration of Helsinki. Written informed consent was required and a sample of the Informed Consent Form (ICF) is provided. A listing of all investigators and their qualifications is provided in a CSR Appendix. The meetings conducted for the training of investigators is documented in the CSR. In response to a request for additional information the materials used to training investigators was provided by the sponsor (submission e0003). The results of audits of selected sites for evidence that the above assertions are true are included in 4.1

Financial Disclosure

Both AbbVie and Biogen Idec were involved in the studies covered by this application and therefore both signed one Financial Certification Form 3454 and one Financial Disclosure Form 5455 for each of the 8 covered studies. Each sponsor provided a list of investigators with no or missing financial interest and no or missing information regarding payments from the sponsor in these studies. For Study 201 there were 87 investigators at 28 sites whose information was missing. For Study 301 there were only 14 investigators at 12 sites with missing financial information.

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For Study 201, significant payments of other sorts (SPOOS) totaling \$1,360,075 were made to 15 investigators at 14 sites. The total number of subjects randomized by these sites was 57 out of the total of 621. The (b) (6) site on the list (b) (6) received 125,555 in payments. There appears to be no relationship between the payments and the number of patients randomized.

For Study 301 total payments of \$3,317,272 were made to 95 investigators at 73 sites. These sites randomized a total of only 46 patients. The (b) (6) site on this list, (b) (6) received \$173,880 in payments. There appears to be no relationship between the payments and the number of patients randomized.

Both sponsors have submitted a Financial Disclosure Memo indicating that any bias due to the financial payments was minimized by the central randomization method used in these studies, by the double blind, double dummy design and by the use of blinded assessors for the key endpoints. An independent and blinded independent committee was used to adjudicate the primary endpoint events. An independent and blinded vendor provided all of the imaging assessments.

Patient Disposition

Informed consent was obtained from 1841 patients at the screening visit. All 1841 subjects who signed informed consent were randomized and received at least one dose of study medication. The intent to treat population is composed of these 1841 subjects.

First subject dosed: 11 May 2010

Last Patient Last Treatment Visit: 5 March 2014 (last date for collection of relapses)

Last Follow-up Visit: 28 July 2014

Database lock: 16 September 2014

Patients were randomized at 245 sites in 28 countries, 922 subjects to treatment with Avonex and 919 to treatment with DAC HYP. There were 57 sites in Region 1 which randomized 236 subjects (12.8%), 75 sites in Region 2 which randomized 417 subjects (22.7%) and 113 sites in Region 3 which randomized 1188 subject (64.5%)³.

³ Region 1: United States, Canada.

Region 2: Australia, Denmark, Finland, France, Germany, Greece, Ireland, Israel, Italy, Spain, Sweden, Switzerland, United Kingdom.

Region 3: Argentina, Brazil, Czech Republic, Georgia, Hungary, India, Mexico, Republic of Moldova, Poland, Romania, Russian Federation, Serbia, Ukraine.

Table 4: Reviewer Table: Number randomized by region and treatment group

Geographical Region	150 mg DAC HYP and Avonex placebo	30 ug Avonex and DAC HYP placebo	Subjects
Region 1	118 (12.84%)	118 (12.80%)	236 (12.82%)
Region 2	210 (22.85%)	207 (22.45%)	417 (22.65%)
Region 3	591 (64.31%)	597 (64.75%)	1188 (64.53%)
Total Subjects	919 (100.00%)	922 (100.00%)	1841 (100.00%)

Source: Geographic region 3 by ARM Study301.xls from ADSIT301.jmp

Reviewer Comment: For Study 301 subjects from the United States and Canada represented just over 10% of the study population. None of the 621 subjects randomized in Study 201 were from the United States or Canada.

Treatment completion

Twelve hundred and ninety-seven (1297, 70.5%) subjects were reported as having completed assigned treatment, i.e. completed treatment to the Last Scheduled Treatment Visit (SAP section 6.3.2) which could have been from 96 to 140 weeks after the start of treatment. There were 653 in the DAC HYP group (71.1%) and 644 (69.8%) in the Avonex group who completed the blinded treatment period. This is supported by an analysis of the number of weeks on treatment in period one by completion status in Figure 5 below.

Table 5: Reviewer Table: Number of weeks on treatment for subjects who did or did not complete the double blind treatment period, ITT.

Planned treatment	Total	Weeks on Treatment									
		Number		Mean		Std Dev		Min		Max	
Completer		N	Y	N	Y	N	Y	N	Y	N	Y
150 mg DAC HYP	919	266	653	56.1	120.7	34.8	17.2	0.1	88.3	136.3	145.3
30 ug Avonex	922	278	644	47.1	123.6	35.2	17.5	0.1	92.1	140.0	146.1

Source: Study 301ADSL TR01WKS By (TRT01P and CMPT01FL).xlsx

The completion rate did vary somewhat by region as seen in Table 6 below. The rates were balanced in each region by treatment assignment.

Table 6: Reviewer table: the proportion of subjects who completed treatment by region, ITT.

Planned Treatment	Geographical Region	N	Y	Subjects
150 mg DAC HYP	Region 1	55 (46.6%)	63 (53.4%)	118 (100.0%)
	Region 2	73 (34.8%)	137 (65.2%)	210 (100.0%)
	Region 3	138 (23.4%)	453 (76.6%)	591 (100.0%)
30 ug Avonex	Region 1	52 (44.1%)	66 (55.9%)	118 (100.0%)
	Region 2	74 (35.7%)	133 (64.3%)	207 (100.0%)
	Region 3	152 (25.5%)	445 (74.5%)	597 (100.0%)
Total subjects		544 (29.5%)	1297 (70.5%)	1841 (100.0%)

Source: JReview CrossTab 205MSADSL: Trt compl flag by TRT01P and RGN row percent.xls

The most common reason for premature discontinuation of treatment was an adverse event (Table 7). This was slightly more common in the DAC HYP group (142 subjects; 15.5%) compared to the Avonex group (12.1%; 112 subjects). Withdrawal of consent was more common in the Avonex group (11.1%; 102 subjects) compared to the DAC HYP group (6.5%; 60 subjects). The remainder of the reasons for discontinuation of treatment did not differ by treatment group.

Table 7: Reviewer table: Standardized disposition term at End of Treatment Visit by treatment group

Standardized Disposition Term	150 mg DAC HYP	30 ug Avonex	All Subjects
COMPLETED	653 (71.1%)	644 (69.8%)	1297 (70.5%)
ADVERSE EVENT	142 (15.5%)	112 (12.1%)	254 (13.8%)
CONSENT WITHDRAWN	60 (6.5%)	102 (11.1%)	162 (8.8%)
OTHER	42 (4.6%)	29 (3.1%)	71 (3.9%)
INVESTIGATOR DECISION	11 (1.2%)	17 (1.8%)	28 (1.5%)
LOST TO FOLLOW-UP	8 (0.9%)	8 (0.9%)	16 (0.9%)
DISEASE PROGRESSION, AS DEFINED BY THE PROTOCOL	3 (0.3%)	7 (0.8%)	10 (0.5%)
DEATH	0 (0.0%)	3 (0.3%)	3 (0.2%)
TOTAL	919 (100.1%)	922 (99.9%)	1841 (100.0%)

Source: JReview CrossTab DSDECOD by Planned TRT group filter DSCAT_Dispev DSSCAT_EOT.xls

When examined by region, the primary reason for premature discontinuation of treatment remained an adverse event followed by withdrawal of consent (Table 8). No single reason for

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treatment discontinuation accounts for the higher proportion of non-completers in Region 1⁴. The increased number of discontinuations due to an adverse event in the DAC HYP group in Regions 2 and 3 is not apparent in Region 1. The increased number of treatment discontinuations due to withdrawal of consent seen in Regions 2 and 3 is not apparent in Region 1.

⁴ Region 1: United States, Canada.

Region 2: Australia, Denmark, Finland, France, Germany, Greece, Ireland, Israel, Italy, Spain, Sweden, Switzerland, United Kingdom.

Region 3: Argentina, Brazil, Czech Republic, Georgia, Hungary, India, Mexico, Republic of Moldova, Poland, Romania, Russian Federation, Serbia, Ukraine.

Table 8: Reviewer Table. Reason for discontinuation from treatment by Region and Planned treatment as reported by investigator

DSDECOD	Total	Region 1				Region 2				Region 3			
		150 mg DAC HYP		30 ug Avonex		150 mg DAC HYP		30 ug Avonex		150 mg DAC HYP		30 ug Avonex	
		N	%	N	%	N	%	N	%	N	%	N	%
COMPLETED	1297	63	53.4%	66	55.9%	137	65.2%	133	64.3%	453	76.6%	445	74.5%
ADVERSE EVENT	254	22	18.6%	21	17.8%	48	22.9%	36	17.4%	72	12.2%	55	9.2%
CONSENT WITHDRAWN	162	14	11.9%	15	12.7%	10	4.8%	21	10.1%	36	6.1%	66	11.1%
DEATH	3	0	0.0%	0	0.0%	0	0.0%	0	0.0%	0	0.0%	3	0.5%
DISEASE PROGRESSION, AS DEFINED BY THE PROTOCOL	10	2	1.7%	3	2.5%	1	0.5%	2	1.0%	0	0.0%	2	0.3%
INVESTIGATOR DECISION	28	5	4.2%	4	3.4%	4	1.9%	8	3.9%	2	0.3%	5	0.8%
LOST TO FOLLOW-UP	16	3	2.5%	5	4.2%	1	0.5%	0	0.0%	4	0.7%	3	0.5%
OTHER	71	9	7.6%	4	3.4%	9	4.3%	7	3.4%	24	4.1%	18	3.0%
TOTAL	1841	118	100.0%	118	100.0%	210	100.0%	207	100.0%	591	100.0%	597	100.0%

Source: DSSCAT=EOT Subset of DSCAT= Disp Event Subset of Join Study 301 DS with ADSL (2) By (DSDECOD).xlsx and DSSCAT=EOT Subset of DSCAT= Disp Event Subset of Join Study 301 DS with ADSL (2) By (DSDECOD).jmp

Reviewer Comment: The overall proportion of subjects who completed the treatment is reasonable considering that completion was defined as having completed at least 96 weeks of treatment. However there appears to be a significant difference in the completion

rate by region. The rate is just over 50% in Region 1 (the US and Canada) compared to 75% for Region 3. The rates are balanced by treatment arm. The reasons for premature discontinuation of treatment are also balanced between the two treatment groups. The differences in the completion rate and reasons for discontinuation are not likely to have had an effect on outcome measures. The sponsor reports that the reduction in ARR was not statistically significant in Region 1 although the point estimate favors DAC HYP (Study 301 CSR Table 149, page 864/3937). See the review by Dr. Ling for the interaction of site or region on the key efficacy analyses. These differences could indicate differences in treatment patterns outside the US and do to some extent raise a question as to whether the results of the study can be extrapolated to the population of patients with MS in the US.

Reclassification of reasons for discontinuation from treatment

The reasons for discontinuation from the study were initially reported and were listed above as they were recorded by the investigator on the case report forms.

The sponsor reclassified the reasons for study discontinuation prior to unblinding as described in Statistical Analysis Plan (Section 6.3.2). As part of the reclassification, discontinuations due to an adverse event with the term “Multiple Sclerosis Relapse” and which led to discontinuation of treatment were mapped programmatically to the Lack of Efficacy category. Discontinuations of treatment due to “disease progression, as defined by the protocol” were also reclassified as “Lack of Efficacy”. Discontinuations due to personal or logistical reasons were reclassified as “Consent Withdrawn”. Other reclassifications were based on a review of the text recorded by the investigator in the CRF and submitted in the SUPPDS domain.

Table 9: Reviewer Table: Reclassified reasons for discontinuation of Treatment

Disposition Category	Randomized N, (%)	150 mg DAC HYP N, (%)	30 ug Avonex N, (%)
COMPLETED	1297 (70.5%)	653 (71.1%)	644 (69.8%)
ADVERSE EVENT	213 (11.6%)	130 (14.1%)	83 (9.0%)
CONSENT WITHDRAWN	127 (6.9%)	49 (5.3%)	78 (8.5%)
LACK OF EFFICACY	99 (5.4%)	31 (3.4%)	68 (7.4%)
PERSONAL / LOGISTICAL	32 (1.7%)	19 (2.1%)	13 (1.4%)

Disposition Category	Randomized N, (%)	150 mg DAC HYP N, (%)	30 ug Avonex N, (%)
OTHER - PREGNANCY	19 (1.0%)	12 (1.3%)	7 (0.8%)
OTHER - NONCOMPLIANCE	18 (1.0%)	10 (1.1%)	8 (0.9%)
LOST TO FOLLOW-UP	15 (0.8%)	5 (0.5%)	10 (1.1%)
INVESTIGATOR DECISION	10 (0.5%)	5 (0.5%)	5 (0.5%)
OTHER - SITE CLOSURE	8 (0.4%)	5 (0.5%)	3 (0.3%)
DEATH	3 (0.2%)	0 (0.0%)	3 (0.3%)
TOTAL	1841	919	922

Source: DSSCAT=EOT Subset of DSCAT= Disp Event Subset of Join Study 301 DS with ADSL (2) By (TRT01RE2).xlsx

Following reclassification discontinuation was due to an adverse event in 130 subjects (14%) in the DAC HYP group and to 83 (9%) in the Avonex group, i.e. about twice as common in the DAC HYP group. The new category of “Lack of Efficacy” includes 31 subjects (3%) treated with DAC HYP vs. 68 (7%) treated with Avonex. Since a relapse resulting in discontinuation of treatment is now included in “Lack of Efficacy” and since relapses were more frequent in the Avonex group, “Lack of Efficacy” is now more frequent in the Avonex group.

Reviewer Comment: In the AE dataset there are 282 AEs in 282 subjects that had an action taken of “drug withdrawn”. 40 had an AEDECOD of “Multiple sclerosis relapse”. There were 12 discontinuations due to an adverse event (DAE) of MS relapse in the DAC HYP group and 28 in the Avonex group.

When the reclassified reasons for discontinuation of treatment are examined by region, there is still no single reason that accounts for the overall high rate of discontinuation in region 1. The increased frequency of discontinuation of treatment in subjects treated with DAC HYP is apparent in all regions but still most prominent in Regions 2 and 3. Lack of efficacy is more frequent in subjects treated with Avonex for all regions although this reason for discontinuation of treatment is much less frequent in Region 3 compared to the other 2 regions.

Table 10: Reviewer Table: Reclassified reasons for discontinuation of treatment, by region.

Disposition Recategory	Randomized (n)	Region 1		Region 2		Region 3	
		150 mg DAC HYP	30 ug Avonex	150 mg DAC HYP (n)	30 ug Avonex (n)	150 mg DAC HYP (n)	30 ug Avonex (n)
		N, % of randomized in Region					
COMPLETED	1297 (70.5%)	63 (53.4%)	66 (55.9%)	137 (65.2%)	133 (64.3%)	453 (76.6%)	445 (74.5%)
ADVERSE EVENT	213 (11.6%)	22 (18.6%)	15 (12.7%)	41 (19.5%)	20 (9.7%)	67 (11.3%)	48 (8.0%)
CONSENT WITHDRAWN	127 (6.9%)	9 (7.6%)	10 (8.5%)	13 (6.2%)	19 (9.2%)	27 (4.6%)	49 (8.2%)
LACK OF EFFICACY	99 (5.4%)	7 (5.9%)	15 (12.7%)	12 (5.7%)	29 (14.0%)	12 (2.0%)	24 (4.0%)
PERSONAL / LOGISTICAL	32 (1.7%)	9 (7.6%)	5 (4.2%)	0 (0.0%)	0 (0.0%)	10 (1.7%)	8 (1.3%)
OTHER - PREGNANCY	19 (1.0%)	3 (2.5%)	1 (0.8%)	3 (1.4%)	2 (1.0%)	6 (1.0%)	4 (0.7%)
OTHER - NONCOMPLIANCE	18 (1.0%)	1 (0.8%)	0 (0.0%)	3 (1.4%)	1 (0.5%)	6 (1.0%)	7 (1.2%)
LOST TO FOLLOW-UP	15 (0.8%)	1 (0.8%)	6 (5.1%)	1 (0.5%)	1 (0.5%)	3 (0.5%)	3 (0.5%)
INVESTIGATOR DECISION	10 (0.5%)	3 (2.5%)	0 (0.0%)	0 (0.0%)	2 (1.0%)	2 (0.3%)	3 (0.5%)
OTHER - SITE CLOSURE	8 (0.4%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	5 (0.8%)	3 (0.5%)
DEATH	3 (0.2%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	3 (0.5%)

Disposition Recategory	Randomized (n)	Region 1		Region 2		Region 3	
		150 mg DAC HYP	30 ug Avonex	150 mg DAC HYP (n)	30 ug Avonex (n)	150 mg DAC HYP (n)	30 ug Avonex (n)
		N, % of randomized in Region					
TOTAL	1841 (100.0%)	118 (100.0%)	118 (100.0%)	210 (100.0%)	207 (100.0%)	591 (100.0%)	597 (100.0%)

Source: DSSCAT=EOT Subset of DSCAT= Disp Event Subset of Join Study 301 DS with ADSL (2) By (TRT01RE2 - Trt Disposition Recategory in Period 01).jmp and DSSCAT=EOT Subset of DSCAT= Disp Event Subset of Join Study 301 DS with ADSL (2) By (TRT01RE2).xlsx

Since subjects randomized to Avonex who had been treated previously with any interferon β may have recognized their treatment assignment by recognition of the typical injection-related adverse events, the influence of previous treatment with any interferon or specifically with interferon β 1a on treatment completion rate is assessed in Table 11 and Table 12.

Table 11: Reviewer table: Treatment completion by any previous treatment for MS (except corticosteroids) and planned treatment, ITT

Treatment Completers Flag			DAC HYP 150 mg				Avonex 30 ug			
	Total		No previous treatment		Previous treatment		No previous treatment		Previous treatment	
	N	%	N	%	N	%	N	%	N	%
N	544	29.5%	142	26.3%	124	32.6%	144	26.4%	134	35.6%
Y	1297	70.5%	397	73.7%	256	67.4%	402	73.6%	242	64.4%
Total	1841	100.0%	539	100.0%	380	100.0%	546	100.0%	376	100.0%

Source: Join Study 301 ADSL for ARR with ADBASE By (CMPT01FL - Treatment Completers Flag in Period 01).xlsx

Table 12: Reviewer table: Treatment completion rate by previous treatment with any interferon β , ITT

Randomization Stratum IFN beta Usage	Study Completers Flag	DAC HYP 150 mg	Avonex 30 ug	Total Subjects
N	N	132 (14.36%)	129 (13.99%)	261 (14.18%)
	Y	479 (52.12%)	482 (52.28%)	961 (52.20%)
Y	N	63 (6.86%)	99 (10.74%)	162 (8.80%)
	Y	245 (26.66%)	212 (22.99%)	457 (24.82%)
	Subjects	919 (100.00%)	922 (100.00%)	1841 (100.00%)

Source: JRevCTab ITT RandStratINFBeta CompletersFlag by TRT01P.xls

Reviewer Comment: Despite the potential that subjects previously treated with an interferon may have been able to recognize that they had been randomized to an interferon in the trial, this did not appear to have affected their willingness to complete randomized treatment in the trial.

Study Completion

Those who discontinued treatment but continued in the study agreed to continue assessments for 6 months following the last dose of investigational treatment. Study completion was defined in the SAP (Section 6.3.2) as having completed follow-up to 180 days after the Last Dosing Date. Overall 77% of subjects completed the study, 78.8% of those treated with DAC HYP and 75.3% of those treated with Avonex (Table 13). The reasons for discontinuation of the study were also reclassified but there were relatively few changes.

Table 13: Reviewer table: Standardized disposition term at End of Study Visit by treatment group

Standardized Disposition Term	150 mg DAC HYP and Avonex placebo	30 ug Avonex and DAC HYP placebo	Subjects
COMPLETED	724 (78.8%)	694 (75.3%)	1418 (77.0%)
CONSENT WITHDRAWN	82 (8.9%)	111 (12.0%)	193 (10.5%)
ADVERSE EVENT	63 (6.9%)	64 (6.9%)	127 (6.9%)
OTHER	27 (2.9%)	24 (2.6%)	51 (2.8%)
LOST TO FOLLOW-UP	11 (1.2%)	11 (1.2%)	22 (1.2%)
INVESTIGATOR DECISION	11 (1.2%)	8 (0.9%)	19 (1.0%)
DISEASE PROGRESSION, AS DEFINED BY THE PROTOCOL	1 (0.1%)	6 (0.7%)	7 (0.4%)
DEATH	0 (0.0%)	4 (0.4%)	4 (0.2%)
Total	919 (100.0%)	922 (100.0%)	1841 (100.0%)

Source: DSDECOD by Plnd TRT filter DSCAT_DispEv DSSCAT_EOS.xls (JReview CrossTab)

Protocol Violations/Deviations

Protocol deviations that may have affected data integrity or patient safety were categorized as “major” and occurred in 66% of subjects treated with DAC HYP and 65% of those treated with Avonex.

Table 14: Reviewer Table: Major protocol deviations by treatment group.

Subcategory for Protocol Deviation	DAC HYP 150 mg	Avonex 30 ug	All Subjects
01-Informed Consent	299 (32.54%)	294 (31.89%)	599 (32.54%)
02-Eligibility	29 (3.16%)	25 (2.71%)	54 (2.93%)
03-Study Tx Administration	148 (16.10%)	144 (15.62%)	292 (15.86%)
04-Prohibited Con Med	52 (5.66%)	44 (4.77%)	96 (5.21%)
05-Key Study Procedure	244 (26.55%)	262 (28.42%)	506 (27.49%)
06-Other	244 (26.55%)	253 (27.44%)	498 (27.05%)
Total Subjects	919 (100.00%)	922 (100.00%)	1841 (100.00%)

Source: JReview crosstab - Subcat of DV DVSCAT from DS by trt01 filter for major or Major.xls

54 subjects had 55 major protocol deviations related to eligibility, 29 in the DAC HYP group and 25 in the Avonex group. 11 subjects in the DAC group and 6 in the Avonex group did not meet inclusion criterion #5 related to recent disease activity. Only one subject in each group had a deviation related to inclusion criterion #3, i.e. did not meet the McDonald criteria for a confirmed diagnosis of MS. One subject in the DAC HYP group and 4 in the Avonex group entered the trial with a baseline EDSS greater than 5.0. Three subjects in the DAC HYP group and 4 in the Avonex group had a relapse within 50 days (exclusion 11) or had been treated with IV or oral corticosteroids or with glatiramer acetate within 30 days (exclusion 24).

292 subjects had 424 major protocol deviations related to study drug administration, 219 deviations in 148 subjects in the DAC HYP group and 205 deviations in 144 subjects in the Avonex group.

506 subjects had 823 major protocol deviations related to key study procedures, 376 in 244 subjects in the DAC HYP group and 447 in 262 subjects in the Avonex group.

96 subjects had 127 major protocol deviations related to prohibited concomitant medications, 62 protocol deviations in 52 subjects in the DAC HYP group and 65 deviations in 44 subjects in the Avonex group. The text in the “DVTERM” field contained “steroids” in 9 subjects and contained the term “relapse” in 27 subjects. – see tables for other steroid or relapse related terms.

Serious GCP violations were found at two sites.

Site 235 in Brazil (Region 3) had randomized 11 subjects, 6 to DAC HYP 150 mg and 5 to Avonex 30 µg. This site was terminated due to “significant GCP violations”. All subjects had an early termination visit. Six patients were randomized to DAC HYP 150 mg and 5 to Avonex 30 µg. One subject in the DAC HYP arm had 4 relapses and one subject in the Avonex arm had 2 relapses. One subject in the Avonex arm had a progression of disability.

Site 453 (Italy, Region 2) was also noted to have significant GCP violations but all subjects had completed study treatment at the time that this was discovered. This site had randomized 40 subjects, 21 to DAC HYP 150 mg and 19 to Avonex 30 µg. 11 subjects in the Avonex arm had 20 relapses and 5 subjects in the DAC HYP arm had 5 relapses.

The sponsor conducted key efficacy analyses excluding subjects from either or both of these sites. No difference in efficacy results was found.

Reviewer Comment: This reviewer has assessed the influence of the two sites with serious GCP violations and agrees with the sponsor’s conclusions that these two sites did not affect the study results. Subjects from these sites are included in the full ITT by both the sponsor and this reviewer.

In general the types and frequency of protocol deviations are not unexpected in a large trial. These were balanced between the treatment arms and do not appear to influence the primary efficacy and safety conclusions of the trial. The sponsor had provided all key analyses including and excluding the above 2 sites. There was no impact on study results.

Table of Demographic Characteristics

Approximately 90% of the population studied was white. As expected for a population with MS, slightly less than 70% were female. The mean age of the population was 36 years. Only two subjects were over 55 years old and only 39 were less than 20 years old.

Table 15: Reviewer table: Demographic characteristics of the ITT Population

Demographic Parameters	Treatment Group		Total (N=1841) n (%)
	DAC HYP 150 mg (N= 919) n (%)	Avonex 30 µg (N= 922) n (%)	
Sex			
Male	294 (33)	295 (32)	589 (32)
Female	625 (68)	627 (68)	1252 (68)
Age			
Mean years (SD)	36.4 (9.4)	36.2 (9.3)	36.3 (9.3)
Median (years)	36	36	36

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Demographic Parameters	Treatment Group		Total (N=1841) n (%)
	DAC HYP 150 mg (N= 919) n (%)	Avonex 30 µg (N= 922) n (%)	
Min, max (years)	18, 56	18, 56	18, 56
Age Group			
18-19	14 (1.52)	25 (2.71)	39 (2.12)
20-29	236 (25.68)	227 (24.62)	463 (25.15)
30-39 years	322 (35.04)	327 (35.47)	649 (35.25)
40-49 years	250 (27.20)	256 (27.77)	506 (27.49)
50 - 55 years	96 (10.45)	86 (9.33)	182 (9.89)
> 55 years	1 (0.11)	1 (0.11)	2 (0.11)
Race			
White	823 (89.55%)	828 (89.80%)	1651 (89.68%)
Black or African American	13 (1.41%)	12 (1.30%)	25 (1.36%)
Asian	27 (2.94%)	28 (3.04%)	55 (2.99%)
American Indian or Alaska Native	0 (0.00%)	1 (0.11%)	1 (0.05%)
Not Reported Due To Confidentiality Regulations	29 (3.16%)	25 (2.71%)	54 (2.93%)
Other ¹	27 (2.94%)	28 (3.04%)	55 (2.99%)

¹ Data on race and/or ethnicity were not collected because of local regulations.

Approximately 65% of subjects were randomized in Region 3 which included sites in Eastern Europe and South America. Twenty-three percent of the subjects were randomized in Region 2 which included sites in Western Europe. Only 13% of subjects were randomized in the US and Canada. There were no differences in the basic demographic characteristics such as age and sex between the three regions.

Table 16: Reviewer Table: Number randomized by region and treatment group

Geographical Region Group	150 mg DAC HYP and Avonex placebo	30 ug Avonex and DAC HYP placebo	Subjects
Region 1	118 (12.84%)	118 (12.80%)	236 (12.82%)
Region 2	210 (22.85%)	207 (22.45%)	417 (22.65%)
Region 3	591 (64.31%)	597 (64.75%)	1188 (64.53%)
Total Subjects	919 (100.00%)	922 (100.00%)	1841 (100.00%)

Source: Geographic region 3 by ARM Study301.xls from ADSIT301.jmp

Region 1 = Canada and USA

Region 2 = AUS (AUSTRALIA), ISR (ISRAEL), GERMANY (DEU), DENMARK (DNK), SPAIN (ESP), FINLAND (FIN), FRANCE (FRA), GREAT BRITAIN (GBR), GREECE (GRC), IRELAND (IRL), ITALY (ITA), SWEDEN (SWE)

Region 3 = CZECH REPUBLIC (CZE), HUNGARY (HUN), GEORGIA (GEO), MOLDOVA (MDA), POLAND (POL), ROMANIA (ROU), RUSSIAN FEDERATION (RUS), SERBIA (SRB), UKRAINE (UKR), INDIA (IND), ARGENTINA (ARG), BRAZIL (BRA), MEXICO (MEX)

Other Baseline Characteristics (e.g., disease characteristics, important concomitant drugs)

At baseline the clinical aspects of MS were generally typical of relapsing MS and balanced between the two treatment groups. Nearly 85% of subjects in the trial fulfilled the clinical criteria for dissemination of attacks in time and space without the need for support from the MRI scan (McDonald criterion 1). Only about 6% had a diagnosis based on one clinical attack (criteria 3 and 4).

Table 17: Reviewer Table: Baseline McDonald Criteria

Baseline McDonald Criteria	150 mg DAC HYP	30 ug Avonex	Subjects
1	784 (42.59%)	776 (42.15%)	1560 (84.74%)
2	83 (4.51%)	87 (4.73%)	170 (9.23%)
3	31 (1.68%)	31 (1.68%)	62 (3.37%)
4	21 (1.14%)	28 (1.52%)	49 (2.66%)
Total Subjects	919 (49.92%)	922 (50.08%)	1841 (100.00%)

Source: JRev Baseline McDonald criteria from Baseline and Disease by Planned Treatment in Period 1 from ADSL and BL McD criteria by Trt01.xls

Both clinical disease activity and lesion activity on MRI scan were well balanced between the two treatment arms.

Table 18: Reviewer Table: Clinical and MRI characteristics of MS at baseline by planned treatment in period 1, ITT

Planned Treatment	Time Since Onset of the Symptoms Years				
	Subjects, n	mean	std.dev.	min	max
150 mg DAC HYP	919	6.96	6.27	0	36
30 ug Avonex	922	6.92	6.28	0	45
Time Since Diagnosis Years					
150 mg DAC HYP	919	4.20	4.97	0	27
30 ug Avonex	922	4.11	4.70	0	26
Time since most recent pre-study relapse, mos					
150 mg DAC HYP	919	5.43	3.41	1	32
30 ug Avonex	922	5.14	3.25	0	24
Number of Relapses Within the Past Year					
150 mg DAC HYP	919	1.53	0.72	0	5
30 ug Avonex	922	1.58	0.75	0	6
Number of Relapses Within the Past 3 Years					

Planned Treatment	Time Since Onset of the Symptoms Years				
	Subjects, n	mean	std.dev.	min	max
150 mg DAC HYP	919	2.65	1.21	1	15
30 ug Avonex	922	2.68	1.29	1	14
	Gadolinium enhancing lesions at baseline				
150 mg DAC HYP	919	1.98	5.86	0	119
30 ug Avonex	922	2.26	5.85	0	92
	Baseline T1 lesion count				
150 mg DAC HYP	919	31.81	33.91	0	195
30 ug Avonex	922	33.88	34.47	0	208
	Baseline T1 lesion volume				
150 mg DAC HYP	919	3335.51	5328.05	0	49139
30 ug Avonex	922	3450.06	5383.56	0	48587
	Baseline T2 lesion count				
150 mg DAC HYP	919	49.16	35.52	0	221
30 ug Avonex	922	51.82	37.39	1	239
	Baseline T2 lesion volume				
150 mg DAC HYP	919	9660.71	12428.3	0	128481
30 ug Avonex	922	9946.89	11805.8	9	99205

Source: JReview Summary Listing Baseline and Demographic dataset: BL T1 count by Trt01.xls

The baseline level of disability did not differ significantly between the two treatment arms. The mean EDSS score at baseline was approximately 2.5, i.e. the average subject had minimal disability defined as a grade of 2 on two of the EDSS functional scales (Table 19). The distribution of EDSS scores was similar for each treatment group (Table 20).

Table 19: Reviewer Table: Baseline EDSS score by treatment group, ITT

Planned Treatment for Period 01	ESSTRESN - Numeric Result/Finding in Standard Units)					
	ITT, N	Mean	Std Dev	Min	Max	Median
150 mg DAC HYP	919	2.48	1.21	0	5.5	2
30 ug Avonex	922	2.54	1.25	0	6	2.5

Source: Join 205MSADSL with ESBLFL_Y subset of EDSS subset of ESlr incl nonmatch By (TRT01P).xlsx

Table 20: Reviewer Table: Baseline EDSS by treatment group, ITT

Baseline EDSS	150 mg DAC HYP	30 ug Avonex	Total Subjects
0	38 (2.06%)	34 (1.85%)	72 (3.91%)
1	76 (4.13%)	75 (4.07%)	151 (8.20%)
1.5	169 (9.18%)	189 (10.27%)	358 (19.45%)
2	185 (10.05%)	163 (8.85%)	348 (18.90%)
2.5	94 (5.11%)	79 (4.29%)	173 (9.40%)
3	97 (5.27%)	91 (4.94%)	188 (10.21%)

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Baseline EDSS	150 mg DAC HYP	30 ug Avonex	Total Subjects
3.5	101 (5.49%)	112 (6.08%)	213 (11.57%)
4	75 (4.07%)	82 (4.45%)	157 (8.53%)
4.5	49 (2.66%)	41 (2.23%)	90 (4.89%)
5	34 (1.85%)	53 (2.88%)	87 (4.73%)
5.5	1 (0.05%)	2 (0.11%)	3 (0.16%)
6	0 (0.00%)	1 (0.05%)	1 (0.05%)
Total Subjects	919 (49.92%)	922 (50.08%)	1841 (100.00%)

Source: JReview crosstab BL EDSS from Baseline and Disease by Planned Treatment in Period 1 and BL EDSS by Trt01.xls

Previous treatment for MS

Approximately 50% of the subjects had not been treated for MS previously.

Table 21: Reviewer Table: Proportion of subjects with prior treatment for MS by Planned Treatment in Period 1, ITT

Planned Treatment for Period 01	N	Y	Subjects
150 mg DAC HYP	539 (49.68%)	380 (50.26%)	919 (49.92%)
30 ug Avonex	546 (50.32%)	376 (49.74%)	922 (50.08%)
Total Subjects	1085 (100.00%)	756 (100.00%)	1841 (100.00%)

Source: JRev CTab BL Dem dataset Prior Trt Exl Steroids by TRT01P.xls

There does appear to be a difference by region in whether subjects had been treated previously **Table 22**. Only 34% of subjects in Region 1 (Canada and the US) were treatment naïve compared to 63% in Regions 2 and 3. Subjects in Regions 2 and 3 were treatment naïve at a rate nearly twice that of Region 1.

Reviewer Comment: The reason for the difference in previous treatment by Region is not clear but there could have been a greater tendency to enroll treatment naïve patients in Region 2 and 3 compared to Region 1. The higher proportion of subjects who may have failed previous treatment(s) in Region 1 could have played a role in the lower treatment completion rate in Region 1(Table 6).

In principle the treatment effect size could have been affected by the large difference in the proportion of treatment naïve subject in Region 1 but this is unlikely in this study since Region 1 accounts for only about 13% of the subjects randomized and the proportion of treatment naïve subjects in the other 2 Regions is similar at about 63%. See analysis by Dr. Ling as to whether key outcome analyses varied significantly by region.

Table 22: Reviewer table: proportion of subjects with previous treatment for MS by Region, ITT

Geographical Region	N	Y	Subjects
Region 1	80 (33.90%)	156 (66.10%)	236 (100.00%)
Region 2	261 (62.59%)	156 (37.41%)	417 (100.00%)
Region 3	744 (62.63%)	444 (37.37%)	1188 (100.00%)
Total Subjects	1085 (58.94%)	756 (41.06%)	1841 (100.00%)

Source: JRev CTab BlandDem dataset Prior MS trt ex steroids by Region.xls

Of those who had been treated previously approximately 37% had been treated with an interferon and 12% with glatiramer acetate. The types of previous treatment were not significantly different by treatment assignment.

Table 23: Reviewer Table: Previous treatment for MS by treatment group (1% or more of total subjects), ITT

Standardized Medication Name	150 mg DAC HYP	30 ug Avonex	Subjects
INTERFERON BETA-1A	207 (22.5%)	201 (21.8%)	408 (22.2%)
INTERFERON BETA-1B	132 (14.4%)	136 (14.8%)	268 (14.6%)
GLATIRAMER ACETATE	110 (12.0%)	111 (12.0%)	221 (12.0%)
CORTICOSTEROIDS	32 (3.5%)	30 (3.3%)	62 (3.4%)
METHYLPREDNISOLONE	17 (1.8%)	16 (1.7%)	33 (1.8%)
MITOXANTRONE HYDROCHLORIDE	15 (1.6%)	15 (1.6%)	30 (1.6%)
NATALIZUMAB	17 (1.8%)	12 (1.3%)	29 (1.6%)
PLASMAPHERESIS	19 (2.1%)	10 (1.1%)	29 (1.6%)
AZATHIOPRINE	12 (1.3%)	8 (0.9%)	20 (1.1%)
INVESTIGATIONAL DRUG	8 (0.9%)	11 (1.2%)	19 (1.0%)
IMMUNOGLOBULIN G HUMAN	7 (0.8%)	12 (1.3%)	19 (1.0%)
TOTAL SUBJECTS	919 (100.0%)	922 (100.0%)	1841 (100.0%)

Source: JReview Crosstab CMDECOD by Planned treatment in period 1 from ADSL filter CMCAT = MS treatment history; CMDECOD by PLND TRT01 filter CMCAT MS Hx.xls.

However there were differences in the type of previous treatment by Region.

Table 24: Reviewer Table: Previous drug treatment for MS by Region, >1% in any group, ITT

Standardized Medication Name	Region 1	Region 2	Region 3	Subjects
INTERFERON BETA-1A	92 (39.0%)	111 (26.6%)	205 (17.3%)	408 (22.2%)
INTERFERON BETA-1B	35 (14.8%)	38 (9.1%)	195 (16.4%)	268 (14.6%)
GLATIRAMER ACETATE	88 (37.3%)	48 (11.5%)	85 (7.2%)	221 (12.0%)

Standardized Medication Name	Region 1	Region 2	Region 3	Subjects
CORTICOSTEROIDS	7 (3.0%)	6 (1.4%)	49 (4.1%)	62 (3.4%)
METHYLPREDNISOLONE	2 (0.8%)	11 (2.6%)	20 (1.7%)	33 (1.8%)
MITOXANTRONE HYDROCHLORIDE	4 (1.7%)	5 (1.2%)	21 (1.8%)	30 (1.6%)
PLASMAPHERESIS	0 (0.0%)	1 (0.2%)	28 (2.4%)	29 (1.6%)
NATALIZUMAB	14 (5.9%)	10 (2.4%)	5 (0.4%)	29 (1.6%)
AZATHIOPRINE	3 (1.3%)	3 (0.7%)	14 (1.2%)	20 (1.1%)
INVESTIGATIONAL DRUG	2 (0.8%)	2 (0.5%)	15 (1.3%)	19 (1.0%)
IMMUNOGLOBULIN G HUMAN	4 (1.7%)	3 (0.7%)	12 (1.0%)	19 (1.0%)
DIMETHYL FUMARATE	0 (0.0%)	2 (0.5%)	15 (1.3%)	17 (0.9%)
Total randomized in the Region	236 (100%)	417 (100%)	1188 (100%)	1841 (100%)

Source: JRev CTab Conmed ADSL datasets CMDECOD by Region 3 filter CMCAT MS Hx.xls

Reviewer Comment: It appears that a significantly higher proportion of subjects in Region 1 had been treated previously and specifically had more often been treated with interferon β 1a and glatiramer acetate compared to subjects in Region 2 and 3. As seen in Table 10, although the overall treatment completion rate was lower in Region 1 and 2 compared to Region 3, there was no difference in the Avonex group compared to DAC HYP. Therefore the difference may again raise a concern for the overall applicability of the study result to subjects in the US and Canada, but it is unlikely to have affected the treatment effect attributable to DAC HYP.

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

Treatment Compliance

Compliance was monitored for Avonex dosing by documenting the number of units dispensed and those returned. Avonex was administered by the subject at home. DAC HYP was administered in the clinic and documented in the CRF. Table 25 below includes all doses regardless of whether the dose was not administered completely. Compliance was over 80% for both treatment groups and did not differ significantly between the DAC HYP or Avonex treatment groups. Compliance was lowest in Region 1 (Table 26).

Table 25: Reviewer table: Drug compliance* in period one by treatment group, ITT

Planned Treatment	Drug Compliance				
	count subjects	Mean %	std.dev.	Min%	Max%
150 mg DAC HYP	919	88.0	25.2	4.2	104.2
30 ug Avonex	922	83.0	29.9	1.0	101.0

Source: JRev SummTab ADSL Drug Compliance by TRT01P.xls

*: number of injections/number of planned injections

Table 26: Reviewer Table: Drug compliance* in period one by treatment group and region, ITT

Planned Treatment for Period 01	Geographical Region	Drug Compliance in Period 01				
		count subjects	mean	std.dev.	min	max
150 mg DAC HYP	Region 1	118	80.8	28.4	12.5	104.2
	Region 2	210	86	27.4	4.2	104.2
	Region 3	591	90.1	23.3	4.2	104.2
30 ug Avonex	Region 1	118	78.0	32.2	3.1	100
	Region 2	207	78.7	32.5	1.0	100
	Region 3	597	85.50	28.18	1.0	101

Source: JRev SummTab ADSL Drug Compl by TRT01P and RGN.xls

*: number of injections/number of planned injections

Reviewer Comment: The overall compliance rate is reasonable for a study with a two year blinded treatment period. There is no significant difference overall between the two treatment groups. However compliance did seem to differ by region with the lowest in Region 1 and highest in region 3. This appears to correspond to the time of exposure and completion rate by region below.

The number of days from start of treatment to end of treatment in the blinded treatment phase also did not differ by dosing group. See the Clinical Pharmacology review for actual pharmacologic exposure.

Table 27: Reviewer Table: Days on treatment in period one by planned treatment in period one, ITT

Planned Treatment	Days on Treatment				
	count subjects	mean	std.dev.	min	max
150 mg DAC HYP	919	714.3	263.5	1	1017
30 ug Avonex	922	703.8	298.7	1	1023

Source: JRev SummTab ADSL DysOnTRT01 by TRT01P.xls

The number of days on treatment during the blinded treatment phase differed by region with the lowest in region one and the highest in region 3. This did not differ by treatment group.

Table 28: Reviewer Table: Days on treatment by planned treatment and by region, ITT

Planned Treatment	Geographical Region	Days on Treatment				
		count subjects	mean	std.dev.	min	max
150 mg DAC HYP	Region 1	118	657.13	304.36	58	991
	Region 2	210	690.06	276.12	1	997
	Region 3	591	734.29	247.77	1	1017
30 ug Avonex	Region 1	118	681.17	329.30	21	1014
	Region 2	207	673.38	313.51	8	1023
	Region 3	597	718.80	286.24	1	1011

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Source: JRev SummTable ADSL DaysOnTrt01 by TRT01P and RGN.xls

The proportion of subjects who completed treatment to week 96 was similar for the two treatment groups. For each region this proportion is balanced by treatment group but as for the overall treatment completion rate, is lowest for Region 3.

Reviewer Comment: The proportion completing treatment to Week 96 is relevant to the key secondary endpoint, proportion with 12 week confirmed disability progression, since only progressions that started on or prior to Week 96 were included in the primary analysis and those without progression were censored at Week 96. The balanced completion rate supports that this endpoint result was not affected by an imbalance in the proportion that completed treatment to that point.

Table 29: Reviewer Table: Treatment completion by Planned Treatment, ITT

Planned Treatment	Treatment Completers N, % randomized
150 mg DAC HYP	653 (71.06%)
30 ug Avonex	644 (69.85%)
Subjects	1297 (70.45%)

Source: JRev CTab ADSL dataset Trt compl FL by TRT01P.xls

The proportion of subjects who completed treatment to week 96 varied by Region with the lowest rate in Region 1 (US and Canada) and the highest in Region 3.

Table 30: Reviewer Table: Treatment completion by Planned Treatment and by Region, ITT

Planned Treatment	Geographical Region	Treatment Completers N, % randomized in region	Total Subjects N, % randomized in region
150 mg DAC HYP	Region 1	63 (53.39%)	118 (100.00%)
	Region 2	137 (65.24%)	210 (100.00%)
	Region 3	453 (76.65%)	591 (100.00%)
30 ug Avonex	Region 1	66 (55.93%)	118 (100.00%)
	Region 2	133 (64.25%)	207 (100.00%)
	Region 3	445 (74.54%)	597 (100.00%)
	Total Subjects	1297 (70.45%)	1841 (100.00%)

Source: JRev CTab ADSL dataset TrtComplFL by TRT01P and RGN.xls

Reviewer Comment: The number of days on treatment in the blinded portion of the trial and the treatment completion rate are reasonable for a trial with a two year treatment period. The

rates do not differ by treatment group. However there is a difference in these rates by region with the lowest rates in region 1 and the highest in region 3. The difference is not likely to have affected the treatment effect attributable to DAC HYP but raises some concern for the comparability of the populations studied in the 3 regions, particularly Region 1, i.e. the US and Canada.

Concomitant Medications

In general the most commonly used concomitant medications during the blinded treatment phase of the trial were anti-inflammatory drugs.

Table 31: Reviewer table: Concomitant medications during the blinded treatment phase of the trial (overall 5% of subjects or more)

Standardized Medication Name	150 mg DAC HYP	30 ug Avonex	Subjects
PARACETAMOL	705 (77.73%)	703 (77.42%)	1408 (76.48%)
IBUPROFEN	307 (33.85%)	374 (41.19%)	681 (36.99%)
METHYLPREDNISOLONE	163 (17.97%)	211 (23.24%)	374 (20.32%)
METHYLPREDNISOLONE SODIUM SUCCINATE	150 (16.54%)	210 (23.13%)	360 (19.55%)
OMEPRAZOLE	146 (16.10%)	183 (20.15%)	329 (17.87%)
AMOXICILLIN	118 (13.01%)	105 (11.56%)	223 (12.11%)
AMOXI-CLAVULANICO	101 (11.14%)	64 (7.05%)	165 (8.96%)
BACLOFEN	67 (7.39%)	94 (10.35%)	161 (8.75%)
POTASSIUM CHLORIDE	63 (6.95%)	82 (9.03%)	145 (7.88%)
VITAMIN D NOS	74 (8.16%)	66 (7.27%)	140 (7.60%)
AZITHROMYCIN	70 (7.72%)	67 (7.38%)	137 (7.44%)
ACETYLSALICYLIC ACID	62 (6.84%)	54 (5.95%)	116 (6.30%)
NAPROXEN	55 (6.06%)	60 (6.61%)	115 (6.25%)
COUGH AND COLD PREPARATIONS	62 (6.84%)	53 (5.84%)	115 (6.25%)
PANTOPRAZOLE	60 (6.62%)	52 (5.73%)	112 (6.08%)
GABAPENTIN	74 (8.16%)	38 (4.19%)	112 (6.08%)
CIPROFLOXACIN	55 (6.06%)	56 (6.17%)	111 (6.03%)
KETOPROFEN	53 (5.84%)	48 (5.29%)	101 (5.49%)
PHYSIOTHERAPY	50 (5.51%)	51 (5.62%)	101 (5.49%)
ASCORBIC ACID	56 (6.17%)	45 (4.96%)	101 (5.49%)
MULTIVITAMIN	43 (4.74%)	51 (5.62%)	94 (5.11%)

Source: JReview crosstab ADCM CMDECOD by Planned treatment in period 1, CMFL = Y, CMCAT = CONMED; and CMDECOD ADCM1 by PLND TRT01 ADCM1 CMFL Y CMCAT CONMED.xls

The most commonly used medications with an indication related to MS were predominantly the NSAIDs, corticosteroids and muscle relaxants, most of which were used more often in the group treated with Avonex.

Reviewer Comment: Use in the above tables is not limited to use just prior to and after the weekly treatment administration (Avonex or Avonex placebo). When limited to an indication related to MS, anti-inflammatory agents and corticosteroids remain the predominant medications used during the blinded treatment phase.

Table 32: Reviewer table: Per subject use of concomitant medications during the trial with an indication related to MS. (Most common or of special interest).

Standardized Medication Name	150 mg DAC HYP	30 ug Avonex	Subjects
PARACETAMOL	252 (27.78%)	306 (33.70%)	558 (30.31%)
METHYLPREDNISOLONE SODIUM SUCCINATE	130 (14.33%)	190 (20.93%)	320 (17.38%)
METHYLPREDNISOLONE	115 (12.68%)	157 (17.29%)	272 (14.77%)
IBUPROFEN	71 (7.83%)	127 (13.99%)	198 (10.76%)
BACLOFEN	29 (3.20%)	44 (4.85%)	73 (3.97%)
TIZANIDINE HYDROCHLORIDE	14 (1.54%)	17 (1.87%)	31 (1.68%)
INTERFERON BETA-1A	14 (1.54%)	10 (1.10%)	24 (1.30%)
NATALIZUMAB	2 (0.22%)	12 (1.32%)	14 (0.76%)
FINGOLIMOD	6 (0.66%)	6 (0.66%)	12 (0.65%)
GLATIRAMER ACETATE	5 (0.55%)	6 (0.66%)	11 (0.60%)
TERIFLUNOMIDE	3 (0.33%)	1 (0.11%)	4 (0.22%)
INTERFERON BETA-1B	1 (0.11%)	2 (0.22%)	3 (0.16%)
CORTICOTROPIN	0 (0.00%)	2 (0.22%)	2 (0.11%)
PLASMAPHERESIS	1 (0.11%)	1 (0.11%)	2 (0.11%)
RITUXIMAB	1 (0.11%)	0 (0.00%)	1 (0.05%)
GLATIRAMER	0 (0.00%)	1 (0.11%)	1 (0.05%)
INTERFERON	0 (0.00%)	1 (0.11%)	1 (0.05%)
Total Subjects	907 (100.00%)	908 (100.00%)	1841 (100.00%)

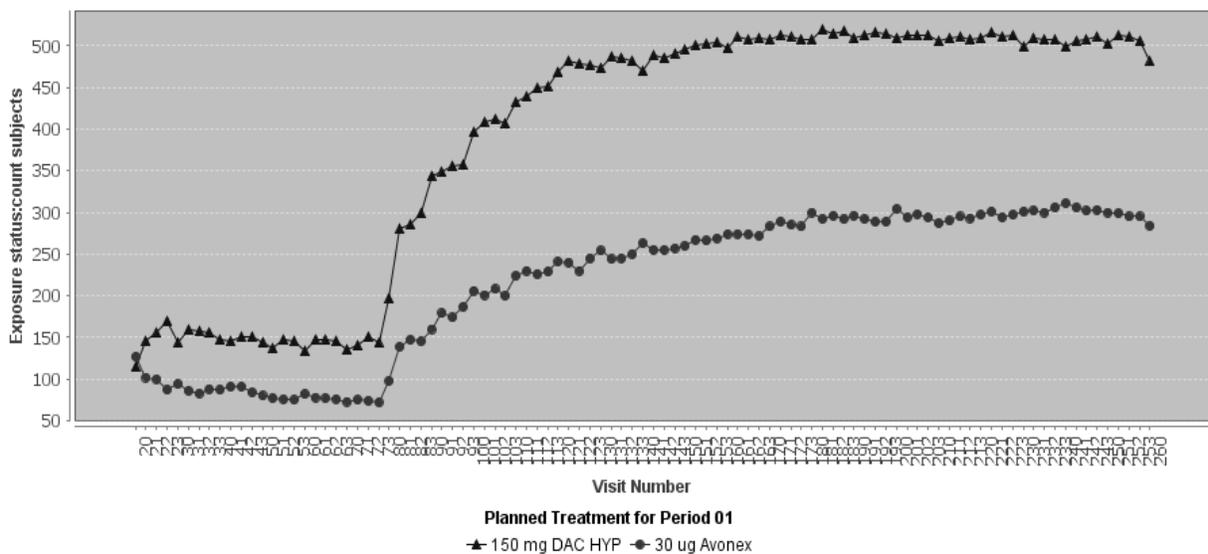
Source: JReview crosstab CMCAT CONMED by Planned treatment in period 01 filter for MS related terms containing "MS", "Multiple" and "Relapse" and CMDECOD from ADCM1 by PLND TRT01 filter MS terms.xls in descending order of DAC HYP column.

Use of NSAIDs

The use of non-steroidal anti-inflammatory drugs during the trial is of interest since these drugs were important to the efforts to blind subjects and investigators to the treatment assignment since injection-related "flu-like" symptoms due to Avonex may have had a tendency to make subjects and/or investigators aware that they were being treated with Avonex, perhaps especially in those who had been treated with an interferon previously. Subjects were instructed to use these drugs, typically either paracetamol or ibuprofen, prior to and for 24 hours after the Avonex/Avonex placebo injection for the first 24 weeks. After 24 weeks their use was at the discretion of the investigator. Thus continued use after 24 weeks could be due to injection-related adverse effects.

The use of NSAIDs before and after administration of the weekly dose of Avonex or Avonex placebo is examined in the following two reviewer figures. Compliance with the instruction to take an NSAID prior to the weekly injection is relatively high for the first 24 weeks although lower for the group receiving Avonex placebo compared to those receiving Avonex. After week 24 the number of subjects not taking an NSAID prior to Avonex/Avonex placebo increases in both treatment groups but is much higher for the Avonex placebo group.

Figure 3: Reviewer Figure: Number of subjects who did not use NSAID prior to injection by visit.

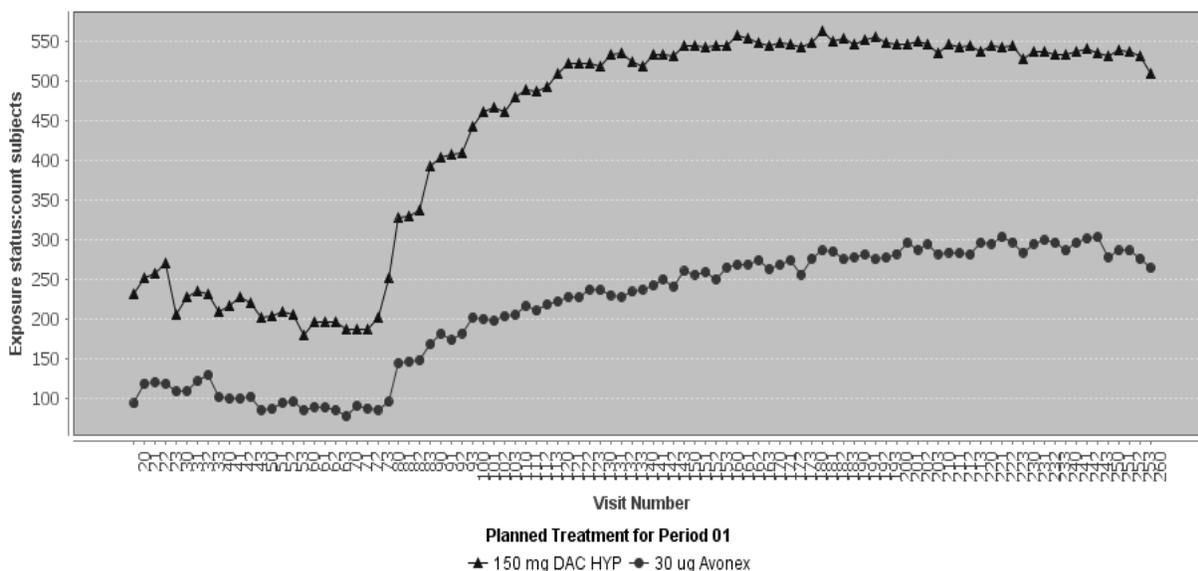


Filter = EXCAT=NSAID; VisitNum<=260; EXSTAT=NOT DONE; Planned time = pre-injection

Source: JReview Line Chart – EX dataset

The number of subjects who did not comply with the instruction to use an NSAID after the weekly injection is higher in the Avonex placebo group than it was pre-injection and again higher in the Avonex placebo group compared to the Avonex group. After week 24 the number of subjects who did not take an NSAID after treatment increases in both treatment groups but much more so for the Avonex placebo group.

Figure 4: Reviewer Figure: Number of subjects who did not use NSAID after injection by visit



Filter = EXCAT=NSAID; VisitNum <=260; EXSTAT=NOT DONE; Planned Time = 24 hours post-injection

Source: JReview Line Chart – EX dataset

Despite the instruction to all subjects to take an NSAID prior to and after each weekly injection for the first 24 weeks there is a difference in compliance between the two treatment groups suggesting that the flu-like symptoms following the use of Avonex was noticeable to many study subjects. When the use of NSAIDs was at the discretion of the investigator, use decreased in both groups but much more so for the Avonex placebo group. The sponsor was asked to provide a comparable analysis. The sponsor’s analysis was provided in sequence e0059 and showed essentially the same results. The sponsor correctly points out that the results indicate that subjects did recognize the need for or lack of need for the use of NSAIDs. This may or may not have led to recognition of treatment assignment. A sensitivity analysis of the ARR excluding subjects with flu-like symptoms did not significantly alter the treatment effect attributable to DAC HYP (Table 90, Study 301 CSR).

The use of corticosteroids during the blinded treatment phase of the trial

The use of corticosteroids for any indication during the blinded treatment phase is displayed in **Table 33**. The percent use did not change significantly when the analysis was limited to the period prior to the start of an alternate treatment for MS.

Table 33: Reviewer table: all corticosteroid use during blinded treatment phase of the trial – all indications, ITT

Steroid Category 1	150 mg DAC HYP	30 ug Avonex	Subjects
LOCAL	245 (13.31%)	117 (6.36%)	362 (19.66%)
SYSTEMIC	349 (18.96%)	430 (23.36%)	779 (42.31%)
Total Subjects	907 (49.27%)	908 (49.32%)	1841 (100.00%)

Source: ITT ADCM1 dataset: STERCAT1 by TRT01P filter CONMED_Y STERFL_Y.xls

Corticosteroid use related to treatment of MS

The number subjects treated for an indication related to MS was higher for those being treated with Avonex (52.9% of subjects) compared to subjects treated with DAC HYP (34.5%). Use included confirmed and unconfirmed relapses as well as for other neurologic symptoms that were suggestive of but determined to not represent a relapse. The difference by treatment group is consistent with a reduction in the number of relapses by DAC HYP.

Table 34: Reviewer Table: Number of subjects treated with systemic corticosteroids for an indication related to MS, ITT (highest 10 indications)

Indication	150 mg DAC HYP N=919	30 ug Avonex N=922	Subjects N=1841
MS RELAPSE	201 (10.9%)	296 (16.1%)	497 (27.0%)
RELAPSE	30 (1.6%)	44 (2.4%)	74 (4.0%)
MS RELAPS	7 (0.4%)	16 (0.9%)	23 (1.2%)
MS-RELAPSE	3 (0.2%)	9 (0.5%)	12 (0.7%)
MULTIPLE SCLEROSIS RELAPSE	4 (0.2%)	7 (0.4%)	11 (0.6%)
RELAPS	4 (0.2%)	4 (0.2%)	8 (0.4%)
RELAPSE OF MS	5 (0.3%)	2 (0.1%)	7 (0.4%)
SM RELAPSE	3 (0.2%)	3 (0.2%)	6 (0.3%)
NON PROTOCOL DEFINED MS RELAPSE	5 (0.3%)	1 (0.1%)	6 (0.3%)
MS RELAPSE 2	0 (0.0%)	5 (0.3%)	5 (0.3%)
TOTAL (% of randomized)	317 (34.5%)	488 (52.9%)	806 (43.8%)

Source: JReview CrossTab: ITT ADCM1 CMINDC by TRT01P filter CM01FL_Y STERCAT1_SYSTEMIC STERFL_Y.xls tab 2

Corticosteroid use not related to treatment of MS

The use of corticosteroids for reasons not related to MS was lower for both treatment groups compared to use for MS, but higher in the DAC HYP group both by number of times

corticosteroids were administered as well as the number of subjects treated. The majority of the indications were related to what appear to be non-neurologic inflammatory conditions. The result is consistent with the increased incidence of these types of adverse events in the DAC HYP group (see Safety Review by Dr. Villalba).

Table 35: Reviewer table: Number of administrations of systemic corticosteroids during the blinded treatment phase of the trial - not related to MS or neurologic symptoms (10 or more uses)

CMINDC - Indication	N(150 mg DAC HYP)	N(30 ug Avonex)	N Rows
TOXIC DERMATITIS	38	0	38
BRONCHITIS	12	5	17
TOXIC DERMATITIT	16	0	16
ELEVATED LIVER ENZYMES	13	0	13
RASH	3	10	13
URTICARIA	6	7	13
CHRONIC SINUSITIS	12	0	12
THROMBOCYTOPENIA	12	0	12
DIFFUSE MACULOPAPULAR ERUPTION/RASH	11	0	11
BACTERIAL INFECTION, VIRAL INFECTION, FUNGAL INFECTION, MULTIORGAN FAILURE, KAWASAKI SYNDROME	10	0	10
VASCULITIS	10	0	10
TOTAL	454	100	554

Source: STERCAT1_Systemic Subset of STERFL_Y Subset of CMCAT CONMED Subset of ADCM1 Ir By (CMINDC - Indication).xlsx (tab 3)

Table 36: Reviewer Table: Number of subjects treated with systemic corticosteroids for an indication not related to MS, ITT (highest 10 indications)

Indication	150 mg DAC HYP	30 ug Avonex	Subjects
URTICARIA	4 (0.2%)	4 (0.2%)	8 (0.4%)
BRONCHITIS	3 (0.2%)	4 (0.2%)	7 (0.4%)
RASH	2 (0.1%)	2 (0.1%)	4 (0.2%)
CONTACT DERMATITIS	3 (0.2%)	1 (0.1%)	4 (0.2%)
COUGH	1 (0.1%)	2 (0.1%)	3 (0.2%)
SINUSITIS	2 (0.1%)	1 (0.1%)	3 (0.2%)
BACK PAIN	2 (0.1%)	1 (0.1%)	3 (0.2%)
PNEUMONIA	2 (0.1%)	0 (0.0%)	2 (0.1%)
ACUTE BRONCHITIS	2 (0.1%)	0 (0.0%)	2 (0.1%)
BRONCHOSPASM	1 (0.1%)	1 (0.1%)	2 (0.1%)
TOTAL (% of randomized)	164 (17.8%)	66 (7.2%)	236 (12.8%)

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Source: JReview CrossTab: ITT ADCM1 CMINDC by TRT01P filter CM01FL_Y STERCAT1_SYSTEMIC STERFL_Y.xls tab 3

Reviewer Comment: In response to a request for additional information the sponsor reported that corticosteroids were used for non-MS indications by 32% of subjects in the DAC HYP group compared to 17% of the Avonex group. Systemic corticosteroids were used for 13% of the DAC HYP group compared to 6% of the Avonex group. The sponsor attributed the difference to the known safety profile of DAC HYP (submitted in sequence e0059).

Efficacy Results – Primary Endpoint

The primary endpoint was the annualized relapse rate (ARR) for the Intent to Treat (mITT) population. The ITT population was defined in the SAP as all randomized subjects who had received at least one dose of any study medication (i.e. a modified ITT). A relapse was defined as new or recurrent neurologic symptoms lasting at least 24 hours, not attributable to fever or infection, that were accompanied by documentation of a new objective neurologic deficit on examination by the Examining Neurologist. The definition of a relapse did not require a minimum increment in neurologic deficit. Only relapses confirmed by the Independent Neurology Evaluation Committee (INEC) were to be included in the primary analysis. New or recurrent symptoms that started less than 30 days after the onset of a protocol-defined relapse and relapses that occurred after the start of an alternate MS therapy were excluded from the analysis. The calculation of ARR is based on the number of days on study as opposed to the number of days on treatment. The number of days on study was calculated from the first dosing date to the date of the End of Treatment Period Visit. The End of Treatment Period Visit was the date of the last scheduled treatment period visit for those who completed or, for those who discontinued treatment prematurely, the date of last follow-up prior to 180 days after the last dose if that date was earlier than the end of treatment visit date. The last dose of study treatment was to occur no later than week 140 and the end of study/end of treatment visit for those who completed was to be at week 144.

Reviewer Comment: Since the validity of the process of identification of relapses is critical to the primary outcome measure and may have an influence on other key measures such as the number of subjects with progression of disability, the process used to identify relapses will be reviewed in some detail.

Subjects who experienced new symptoms were to contact the treating nurse or neurologist within 48 hours. A “standardized Suspected Relapse Questionnaire” was to be completed for each such contact and was to be used to determine whether an Unscheduled Relapse Assessment Visit was necessary.

The protocol did not specify how the Suspected Relapse Questionnaire would be used or any specific criteria for determining whether an unscheduled relapse visit was necessary. Section

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14.3.8 of the protocol states that the “Protocol defined interval to the relapse assessment by the treating neurologist should be no more than 3 days and to the assessment by the examining neurologist to confirm that there was a new objective deficit and to record the EDSS should be no more than 5 days.”

Reviewer Comment: The protocol and SAP do not specifically state that relapses that were not evaluated within the above time frames would be excluded from the analysis.

If the Examining Neurologist confirmed that there was a new objective neurologic deficit then the necessary information was to be sent to the INEC for adjudication. Some of the criteria that had been used to make the determination were recorded on the Suspected Relapse Questionnaire. The subject could be treated with corticosteroids once the Examining Neurologist evaluation was complete.

Based on an initial review of the relapse data it appeared that the information regarding a possible relapse was only collected when a subject was actually seen for a relapse evaluation by the neurologist, i.e. a decision to not evaluate a patient report of a potential relapse was not documented. The protocol and Operations Manual (provided in response to a request for additional information on 19March 2015) also suggest that a subject report of a potential relapse was only to be documented when the investigator had determined that a relapse may have occurred.

The following request for additional information in the “No Filing Review Issues Identified” letter to the sponsor was sent on 5/13/15.

3. Section 14.3.8 of the protocol (Unscheduled Relapse Assessment Visit(s)) states that “subjects who experience new neurological symptoms must contact the Treating Nurse or Treating Neurologist as soon as possible and within no more than 48 hours of the onset of symptoms. A standardized Suspected Relapse Questionnaire will be completed to determine the necessity of an Unscheduled Relapse Assessment Visit.” We located a “Suspected MS Relapse Questionnaire – INEC Alert” form in the site operations manual. However, the instructions for this form state that it “should only be completed if the suspected MS relapse case is sent to INEC for review”. Please indicate whether this questionnaire is the standardized questionnaire used to document all subject reports of possible relapses including those that did not require an unscheduled relapse visit. If not, then indicate where we can find all subject reports of a potential relapse in the CRFs and datasets you submitted.

In response to the above Additional Information Request regarding the Suspected MS Relapse Questionnaire, the sponsor indicated that “the analysis of “subject reported relapses” was not based on the “Suspected MS relapse questionnaire-INEC alert” but rather on subject-reported

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*relapses that resulted in an unscheduled relapse assessment visit". That is, the data from the form was entered in the CRF only if an unscheduled relapse visit was conducted. This is consistent with **Table 37** below which shows that the number of subject contacts recorded was no more than the number of evaluations. If an unscheduled relapse visit was not deemed necessary then the form may have been retained in the site record. Some new neurologic symptoms that were not considered related to a relapse may have been reported as adverse events. In response to a request for additional information the sponsor (submission e0045) provided the original Suspected MS Relapse Questionnaires for selected sites. In general these confirmed that data were not collected for subject reports of new neurologic symptoms that were not considered a "possible MS relapse" by the investigator.*

The results of 1291 questionnaires for 745 subjects and 1291 relapse assessments are provided in the Study 301 RL database. In the same database a determination of whether the subject had a relapse was made by the treating investigator 1304 times for 743 subjects. (There were 17 instances of a relapse assessment without questionnaire results, 10 from the DAC HYP group and 7 from the Avonex group.) This is consistent with the 1304 unscheduled relapse visits.

The treating neurologist determined that 102 subjects had not had a relapse (of 1304 events), 1201 had a relapse and one result was missing. The most common reasons that may have led to the decision that a relapse had not occurred were evidence of severe stress and symptoms of an infection (Table 37).

Table 37: Reviewer Table: Results of the assessments included in the Suspected Relapse Questionnaire, all relapses, ITT

RLTEST	N Rows	Result (in standard units)					
		Missing		No		Yes	
		N	%	N	%	N	%
ANY FEVERS?	1291	2	0.2%	1272	98.5%	17	1.3%
ANY SYMPTOMS OF INFECTION?	1291	2	0.2%	1252	97.0%	37	2.9%
ANY SYMPTOMS OF SEVERE STRESS?	1291	2	0.2%	1243	96.3%	46	3.6%
EXPERIENCED NEW OR RECURRENT NEURO SYMP?	1291	1	0.1%	13	1.0%	1277	98.9%
LAB RESULTS DISPLAY POTENTIAL INFECTION?	1291	142	11.0%	872	67.5%	277	21.5%
LABS COLLECTED DURING RELAPSE ASSESSMNT?	1291	2	0.2%	158	12.2%	1131	87.6%
NEUROLOGIC SIGNS/SYMPTOMS EVOLVED?	1291	1	0.1%	28	2.2%	1262	97.8%

Source: Not primary sx Subset of RLCAT_Questionnaire Subset of Study 301 RL By (RLTEST).xlsx and Not primary sx Subset of RLCAT_Questionnaire Subset of Study 301 RL By (RLTEST).xlsx

Table 38 below lists the sequence of assessments involved in the assessment of a possible relapse.

Table 38: Reviewer table: Steps in the process of relapse evaluation, all relapse evaluations, by planned treatment, ITT.

RLTEST	Total Number of events	Total Number of subjects (% of ITT)	N(150 mg DAC HYP)		N(30 ug Avonex)	
			Number of events	Number of subjects (% of TrtGrp)	Number of events	Number of subjects (% of TrtGrp)
ONSET DATE OF MS RELAPSE SYMPTOMS	1291	739 (40.1%)	519	307 (33.4%)	772	432 (46.9%)
DATE TREATING NEUROLOGIST CONTACTED	1291	739 (40.1%)	519	307 (33.4%)	772	432 (46.9%)
DATE EVALUATED BY TREATING NEUROLOGIST	1304	743 (40.4%)	526	308 (33.5%)	778	435 (47.2%)
HAS THE SUBJECT EXPERIENCED A RELAPSE?	1304	743 (40.4%)	526	308 (33.5%)	778	435 (47.2%)
SUBJECT RELAPSE CONFIRMED BY INEC?	1201	705 (38.3%)	480	290 (31.6%)	721	415 (45.0%)
TREATED WITH IV METHYLPREDNISOLONE?	1304	743 (40.4%)	526	308 (33.5%)	778	435 (47.2%)
TOTAL SUBJECTS		1841 (100.0%)		919 (100.0%)		922 (100.0%)

Source: Join Study 301 RL with ADSL By (RLTEST).jmp and JReview crosstab – Study 301 RL: ITT RLTEST by PLND TRT01 filter ITT01_Y and RLCAT_RL ASSESS.xls

An evaluation was recorded by the Treating Neurologist for 1304 relapses - 526 relapses in 308 subjects in the DAC HYP group and for 778 relapses in 435 subjects in the Avonex group. There were 13 possible relapses (7 in the DAC HYP group and 6 in the Avonex group) occurring in 4 subjects (1 in the DAC HYP group and 3 in the Avonex group) for which there was no onset date or date of contact with the neurologist. A determination was made by the treating neurologist for all 1304 events. Referral to the INEC was made for 1201 of the 1304 events (92.1%). For both treatment groups, all relapses evaluated by the treating neurologist were treated with IV MP regardless of the subsequent INEC adjudication result.

For both treatment groups nearly all of the relapses are included in the first 3 evaluations of a potential relapse.

Table 39: Reviewer table: Number of times a subject was evaluated by the neurologist for a potential relapse by treatment group – ITT in period 1

Group ID	150 mg DAC HYP	30 ug Avonex	Subjects
RELAPSE1	306 (33.3%)	433 (47.0%)	739 (40.1%)
RELAPSE2	124 (3.5%)	203 (22.0%)	327 (17.8%)
RELAPSE3	58 (6.3%)	84 (9.1%)	142 (7.7%)
RELAPSE4	24 (2.6%)	34 (3.7%)	58 (3.2%)
RELAPSE5	10 (1.1%)	14 (1.5%)	24 (1.3%)
RELAPSE6	4 (0.4%)	6 (0.7%)	10 (0.5%)
RELAPSE7	0 (0.0%)	2 (0.2%)	2 (0.1%)
RELAPSE8	0 (0.0%)	1 (0.1%)	1 (0.1%)
RELAPSE9	0 (0.0%)	1 (0.1%)	1 (0.1%)
TOTAL RELAPSES	526	778	1304
SUBJECTS IN ITT - N	919 (100.0%)	922 (100.0%)	1841 (100.0%)

Source: JReview crosstab - RLGRPID by PLND TRT01 filter ITT_01_Y and RLTESTCD_SBEVALDT.xls

An assessment of bias by the investigator or INEC in making the determination that a relapse had occurred

In general, the investigator determined that a relapse had occurred for approximately 90% of relapses evaluated. The proportion did not vary greatly by relapse number or by treatment group. Those in whom the determination was “yes” were to be referred to the INEC for adjudication. Similarly the INEC confirmed that a protocol-defined relapse had occurred for approximately 90% of relapses referred by the investigator for adjudication. This did not vary greatly by relapse number or treatment group.

Reviewer Comment: Because the treating neurologist was aware of subject symptoms and adverse events that might have suggested treatment assignment it is important to assess for any bias in the relapse assessment process. The treating neurologist determined whether a subject report of a potential relapse was to be evaluated at an unscheduled visit and made the decision as to whether an event was to be referred to the INEC. Based on the proportion of events in each treatment arm referred to the INEC there is no indication that the investigator was significantly more or less likely to determine that a subject had a protocol-defined relapse for either treatment group. The same was true of the INEC confirmation process.

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An assessment of the interval between the onset of MS symptoms, contact with the treating neurologist, evaluation by the neurologist

Reviewer Comment: It is important that symptoms of a potential relapse were evaluated soon after onset. If there was a significant delay in subject reporting to the investigator or a delay between subject report and examination by the investigators, the assessments could have resulted in an erroneous determination that a relapse had not occurred and/or the deficit detected may not be representative of the true change related to the relapse.

Subjects were instructed to contact the treating nurse or neurologist within 48 hours of the onset of symptoms (Section 14.3.8 of the protocol). A standardized Suspected Relapse Questionnaire was to be completed to determine the necessity of an unscheduled relapse visit. The data from the form was only entered into the CRF if the treating neurologist determined that an unscheduled visit was necessary.

“Protocol defined interval to the relapse assessment by the treating neurologist should be no more than 3 days (from the onset of the potential relapse) and to the assessment by the examining neurologist to confirm that there was a new objective deficit and to record the EDSS should be no more than 5 days (from the onset of the potential relapse.”

Nearly all subjects (90%) were evaluated by the treating neurologist within 7 days of the subject contacting the site. This interval between subject contact and evaluation by the treating neurologist was 0 days for approximately 70% of the events.

Reviewer Comment: The interval of zero days indicates that 70% of the subjects were evaluated on the same day on which they contacted the site. This is somewhat implausible and raises some doubt about the credibility of the dates and times recorded.

Of greater importance is the interval between the onset of symptoms of a relapse and the evaluation by the treating neurologist. For all relapses the mean interval from the onset of symptoms to evaluation by the treating neurologist was 5.39 ± 5.96 days for the DAC HYP group and 6.04 ± 8.47 days for the Avonex group (Table 40).

Table 40: Reviewer table: Study days from reported onset of relapse symptoms to evaluation by the treating neurologist, all relapses, by planned treatment, ITT

Planned Treatment	N	Study days from RL onset to RL evaluation				
		Mean	Std Dev	Min	Max	Median
150 mg DAC HYP	509	5.39	5.96	0	55	3
30 ug Avonex	763	6.04	8.47	0	83	3

Source: Join join SBEVALDT subset of RL with ADSL with RLONSET match USUBJID and RLGRPID By (TRT01P - Planned Treatment for Period 01).jmp

Approximately 44% of relapses were evaluated more than 3 days after symptom onset, 20% more than 7 days and 1.7% more than 30 days after symptom onset. The proportion of relapses evaluated more or less than 3 days and more or less than 7 days after symptom onset did not differ by treatment group (Table 41).

Table 41: Reviewer table: Summary of the time from relapse symptom onset to evaluation by the treating neurologist by planned treatment in period 1, ITT.

Study days from RL onset to RL evaluation	Total Relapse evaluations		150 mg DAC HYP		30 ug Avonex	
	Number of Relapses	Percent	Number of Relapses	Percent	Number of Relapses	Percent
Missing	15	1.2%	7	1.4%	8	1.0%
3 days or less*	720	56.3%	285	55.2%	435	56.4%
More than 3 days	567	44.4%	231	44.8%	336	43.6%
7 Days or less*	1035	81.0%	424	82.2%	611	79.2%
More than 7 days	252	19.7%	92	17.8%	160	20.8%
Less than 30 days	1265	99.0%	511	99.0%	754	97.8%
30 days or more	22	1.7%	5	1.0%	17	2.2%
TOTAL	1287	100.7%	516	100.0%	771	100.0%

Source: Join join SBEVALDT subset of RL with ADSL with RLONSET match USUBJID and RLGRPID By (Study days from RLSTDY to SBEVALDT).jmp and Study days from RLSTDY to SBEVALDT by TRT01P.xlsx

*: number missing included

Reviewer Comment: The proportion of relapses evaluated beyond the protocol defined time interval did not differ greatly between the two treatment groups and most likely did not affect the analysis of the treatment effect attributable to DAC HYP. However the overall proportion of

relapses that were evaluated beyond 7 days, an interval that DNP has considered the limit for a valid assessment of a relapse, does raise a concern that the clinical features (such as the EDSS score) of a large proportion of the relapses included in the analysis are not representative of the true acute relapse.

The following analyses are intended to explore any potential effect of the time to evaluation of the relapse on the decision by the treating neurologist to refer the event for adjudication and on the confirmation by the INEC. Nearly all relapses were evaluated within 7 days. As seen in Table 42 and Table 43 below, as the time from relapse symptom onset to evaluation increased, there is a slight decline in the proportion of events deemed to be a protocol-defined relapse by the treating neurologist and by the INEC for the DAC HYP treatment group but no decline in the Avonex group.

Table 42: Reviewer table: Proportion of potential relapses evaluated by the treating neurologist and determined to be protocol defined relapses by time since symptom onset and by planned treatment, ITT.

Days from symptom onset to evaluation	N Rows		N(150 mg DAC HYP)		N(30 ug Avonex)	
	Number of Relapses	Yes %	Number of Relapses	Yes %	Number of Relapses	Yes %
3 days or less	670/705	95.0%	265/278	95.3%	405/427	94.8%
More than 3 days	518/567	91.4%	209/231	90.5%	309/336	92.0%
More than 7 days	228/252	90.5%	80/92	87.0%	148/160	92.5%
30 days or more	21/22	95.5%	4/5	80%	17/17	100%

Source: SJEXRLPS Subset of Join 3dys or less subset of SBEVALDT of RL with ADSL with RLOSET match USUBJID and RLGRP.D jmp SJEXRLPS RLSTRESC for 3dys or less RLOSET to SBEVALDT by TRT01P.xlsx

Source: SJEXRLPS Subset of Join More than 3 Day SBEVAL subset of RL with ADSL with RLOSET match USUBJED and RLGRP.D jmp and More than 3 days RLOSET to SBEVALDT by TRT01P.xlsx

Source: SJEXRLPS Subset of Join more than 7 day SBEVALDT with RLOSET with RL match USUBJID and RLGRP.D jmp and More than 7dy RLOSET to SBEVALDT by TRT01P.xlsx

Source: SJEXRLPS Subset of Join 30 day or more Join SBEVALDT with RLOSETDT with RL By (RLORES - Result or Finding in Original Units). jmp

Table 43: Reviewer Table: Proportion of potential relapses confirmed by the INEC by time since symptom onset and by planned treatment, ITT.

Days from symptom onset to evaluation	Total		150 mg DAC HYP		30 ug Avonex	
	Number of Relapses	Yes %	Number of Relapses	Yes %	Number of Relapses	Yes %
3 days or less	620/670	92.5%	244/265	92.1%	376/405	92.8%
More than 3 days	459/518	88.6%	175/209	83.7%	284/309	91.9%
More than 7 days	201/228	88.2%	65/80	81.3%	136/149	91.9%

Days from symptom onset to evaluation	Total		150 mg DAC HYP		30 ug Avonex	
	Number of Relapses	Yes %	Number of Relapses	Yes %	Number of Relapses	Yes %
30 days or more	19/21	90.5%	4/4	100%	15/17	88.2%

Source: INECCONF Subset of Join 3dys or less subset of SBEVALDT of RL with ADSL with RLOSET match USUBJID and RLGRPID.jmp INECCONF RLSTRESC for 3dys or less RLOSET to SBEVALDT by TRT01P.xlsx

Source: INECCONF Subset of Join More than 3 Day SBEVAL subset of RL with ADSL with RLOSET match USUBJED and RLGRPID.jmp and INECCONF result for More than 3 days RLOSET to SBEVALDT by TRT01P.xlsx

Source: INECCONF Subset of Join more than 7 day SBEVALDT with RLOSET with RL match USUBJID and RLGRPID.jmp RLSTRESC for INECCONF subset of more than 7 day SBEVALDT with RLOSET with RL.xlsx

Source: INECCONF Subset of Join 30 day or more Join SBEVALDT with RLOSETDT with RL by RLSTRESC.jmp

Had the proportion referred to the INEC (~95%) and the proportion confirmed by the INEC (~92%) remained the same over time since symptom onset for the DAC HYP group as it did for the Avonex group, then the number of confirmed relapses in the DAC HYP and Avonex groups would have been 460 and 680 respectively compared to 424 and 667 ultimately referred to and confirmed by the INEC. See Table 49 below for an analysis based on the assumption that all assessed relapses were confirmed.

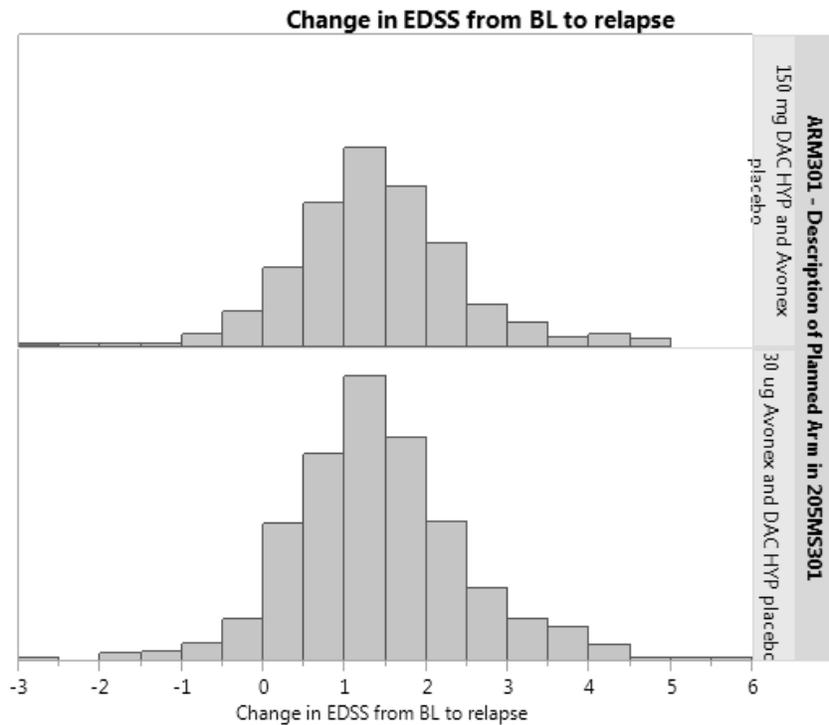
The change in EDSS score at the time of relapse evaluation was assessed to determine what effect the delay from onset to clinical assessment might have had on the status of the relapse at the time the assessments were completed. A measure of the neurologic deficit remaining at the time of the relapse is the change in EDSS score at the time of a relapse compared to the baseline EDSS. The distribution of the change from baseline EDSS to the time of a confirmed relapse is shown in Table 44 and Figure 5 below. The EDSS was assessed at the time of the unscheduled relapse visit.

Table 44: Reviewer Table: Number and proportion of subjects with an increase in EDSS score compared to baseline at the time of an INEC-confirmed relapse, ITT

Change in EDSS from BL to relapse	N Rows		N(150 mg DAC HYP and Avonex placebo)		N(30 ug Avonex and DAC HYP placebo)	
	N	proportion	N	proportion	N	proportion
0.5 or more	1073	0.84	434	0.84	639	0.83
1.0 or more	853	0.66	344	0.67	509	0.66

Source: Join join SJEXRPLPS with EDSS with BL EDSS with TRT from ADSL.jmp and Change in EDSS from BL to RL for SJEXRPLPS by Trt01P.xlsx

Figure 5: Reviewer Figure: Distribution of the change from baseline EDSS at the time of INEC-confirmed relapse by treatment group, ITT.



Reviewer Comment: Despite the delay from symptom onset to clinical evaluation, the EDSS had increased at the time of the relapse by at least 0.5 points in over 80% and by 1 point in about two-thirds of subjects. This is likely to be an underestimate for those with a longer delay to assessment. The proportions do not differ by treatment group. It is not unexpected that the EDSS did not increase for all subjects since only a new objective neurologic deficit was required by the definition of a relapse.

In submission e0030 the sponsor responded to a request for additional information to address the issue of timing between onset of relapse symptoms and the steps in the process of relapse evaluation. The sponsor provided essentially the same analyses and interpretation as those of the reviewer.

To determine whether those relapses not referred to the INEC differed by treatment group, the frequency with which these relapses were reported as an adverse event was evaluated. Of the 106 potential relapses evaluated by the treating neurologists and determined not to be protocol-defined relapses, 45 (42.5%) were reported as an adverse event, 16 (35%) from the DAC HYP group and 29 (48%) from the Avonex group. Of the 1256 events that were considered

by the treating neurologist to represent a protocol-defined relapse, 479 of 506 (94.7%) in the DAC HYP group and 719 of 750 (95.9%) in the Avonex group were reported as AEs. Of the 1639 adverse events with a preferred term of Multiple Sclerosis Relapse, 157 of 658 (23.9%) in the DAC HYP group were considered serious compared to 211 of 981 (21.5%) in the Avonex group.

Table 45: Reviewer table: Adverse event of “Multiple Sclerosis Relapse” by serious vs. not serious and by planned treatment in period one, ITT

AE serious?	All relapses		150 mg DAC HYP		30 ug Avonex	
	N	%	N	%	N	%
N	1271	77.5%	501	76.1%	770	78.5%
Y	368	22.5%	157	23.9%	211	21.5%
Total	1639	100.0%	658	100.0%	981	100.0%

Source: Join MS RL subset of NS subset of Study 301AE with ADSL By (AESER).xlsx

The severity of the adverse event of multiple sclerosis relapse was considered severe for 5% of these events in the DAC HYP group and for 2.7% of those in the Avonex group.

Table 46: Reviewer Table: Adverse event of Multiple Sclerosis Relapse by severity and by planned treatment in period one, ITT

AE severity	Total		150 mg DAC HYP		30 ug Avonex	
	N	%	N	%	N	%
MILD	642	39.2%	247	37.5%	395	40.3%
MODERATE	938	57.2%	378	57.4%	560	57.1%
SEVERE	59	3.6%	33	5.0%	26	2.7%
Total	1639	100.0%	658	100.0%	981	100.0%

Source: Join MS RL subset of NS subset of Study 301AE with ADSL By (AESEV).xlsx

Reviewer Comment: The differences in seriousness or severity between the two treatment groups are minor. There is no indication that the relapses in the DAC HYP group were more or less serious or severe compared to the Avonex group.

Primary Efficacy Endpoint: Annualized Relapse Rate

For the group treated with DAC HYP there were a total of 415 INEC-confirmed relapses that occurred while on study and prior to the start of an alternative treatment for MS (including interferon β). For the group treated with Avonex there were 651 relapses that met the same criteria. For all subjects in the ITT, the sum of days on study or days to the start of an alternative treatment for MS (including interferon β), whichever came first, was 718235 days (1966

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subject-years) for the group treated with DAC HYP and 687481 days (1882 subject-years) for the Avonex group.

Reviewer estimate of the unadjusted annualized relapse rate is 0.211 for the DAC HYP group and 0.346 for the Avonex group.

Table 47: Reviewer table: The total number of relapses that occurred prior to the start of an alternative treatment for MS or prior the end of study days in period one and that were confirmed by the INEC*

Relapse number	DAC HYP 150 mg	Avonex 30 µg
1	254	374
2	88	168
3	43	66
4	19	25
5	7	11
6	4	4
7	0	1
8	0	1
9	0	1
Total	415	651

Source: GroupID by TRT01P - Join RL 1-8 Prior AMS2DT or EOS_Y subset with RL 1 subset RLLORRES_Y INEC

*: The onset date was missing for 12 relapses – 5 in the DAC HYP and 7 for Avonex. None of the 12 was confirmed by the INEC.

The time on treatment was similar for the two treatment groups but the time on study was considerably greater for the DAC HYP treatment group. Calculation of the unadjusted ARR per the SAP was to be based on the time on study.

Table 48: Reviewer Table: Number of days in study in period one or days to start of alternate treatment for MS, whichever came first, ITT

	Days to AltTrtmt else Days to <u>Last treatment</u> in period One +1		Years	Days to AltTrtmt else <u>Days on Study</u> in Period One +1		Years
	N	Sum		N	Sum	
Planned Treatment for Period 01 (TRT01P)						
150 mg DAC HYP	919	654846	1792.87	919	718235	1966.42
30 ug Avonex	922	648889	1776.56	922	687481	1882.22

Source: Sum of Days to AMS2DT else Days to Last treatment in period 1 plus 1 - Study 301 ADSL By (TRT01P - Planned Treatment for Period 01).jmp and Sum of Days to AMS2DT else Days on Study in Period One plus 1 -Study 301 ADSL By (TRT01P - Planned Treatment for Period 01).jmp

Calculation of ARR based on time on study:

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DAC HYP: $(415/718235)*365.25 = 0.211$ (sponsor report – 0.212)

Avonex: $(651/687481)*365.25 = 0.346$ (sponsor report – 0.353)

Reviewer Comment: The reviewer calculated number of relapses and unadjusted relapse rates are comparable to those of the sponsor in Table 29 of the CSR. The sponsor calculation of the adjusted ARR using the negative binomial model adjusted for baseline relapses rate (over 3 years prior to enrollment), baseline EDSS (≤ 2.5 vs. > 2.5) and baseline age (≤ 35 vs. > 35) was 0.216 for the group treated with DAC HYP 150 mg compared to 0.393 for the Avonex group, very similar to the unadjusted rates.

There were 371 relapses that occurred in the DAC HYP group that were prior to the start of alternative treatment for MS or prior to the end of treatment in period one. In the Avonex group there were 606 relapses that met the same criteria. If the time on treatment in period one was used to calculate the ARR it would be 0.207 for the DAC HYP group and 0.341 for the Avonex group.

Reviewer Comment: For the various categories of relapse and using either study days or treatment days the treatment effect consistently favors DAC HYP by 0.133 to 0.146 (Table 49).

Table 49: Reviewer table: Unadjusted ARR by relapse group

Relapse Group	DAC HYP N=919			Avonex N=922			Treatment difference			
	Relapses N	ARR basis		Relapses N	ARR basis		Study Days		Treatment days	
		Study Days	Treatment days		Study Days	Treatment days				
							absolute	relative	absolute	relative
All assessed relapses	526	0.267	0.293	778	0.413	0.438	0.146	35.4%	0.145	33.1%
Relapse per treating neurologist	480	0.244	0.268	721	0.383	0.406	0.139	36.3%	0.138	34.0%
INEC confirmed relapses	424	0.216	0.236	667	0.354	0.375	0.139	39.3%	0.139	37.1%
Prior to EOT and prior to AMS2DT - INEC confirmed	371	0.189	0.207	606	0.322	0.341	0.133	41.3%	0.134	39.3%
Prior to EOS and prior to AMS2DT – INEC confirmed*	415	0.211	0.231	651	0.346	0.366	0.135	39.0%	0.135	36.9%

Source: RLOSET Subset of Join Study 301RL with ADSL.jmp

*: primary analysis population

EOT: Days to end of treatment

EOS: Days to end of study

AMS2DT: Time to start of alternate treatment including β -interferon

Reviewer Comment: The absolute and relative treatment effect attributable to DAC HYP 150 mg is nearly identical for all of the above permutations of relapses included in the analysis and study days versus treatment days. The absolute reduction in the unadjusted ARR varies from 0.133 to 0.146 and the relative reduction is from 33% to 41%.

Subgroup analyses:

Reviewer and sponsor analyses showed no notable differences in the reduction of the ARR by age group or baseline weight. Analyses of ARR by Region are shown below.

Region

The unadjusted ARR did vary somewhat by region. The treatment difference varied from 0.060, a 20.2% reduction in Region 1 to 0.194, a 49.1% reduction in Region 2.

Table 50: Reviewer table: Unadjusted ARR by Region and planned treatment in period one, ITT

	150 mg DAC HYP			30 ug Avonex		
	Region 1 N=118	Region 2 N=210	Region 3 N=591	Region 1 N=118	Region 2 N=207	Region 3 N=597
Days to AMS2DT else time in study	86455	161962	469818	84751	149928	452802
Relapses*	56	89	270	69	162	420
ARR	0.237	0.201	0.210	0.297	0.395	0.339
Treatment difference				0.060	0.194	0.129
Relative ARR reduction				20.2%	49.1%	38.1%

Source: Join RL 1 Prior AMS2DT or EOS_Y subset with RL 1 subset RLOORRES_Y INEC By (TRT01P - Planned Treatment for Period 01 and by RGNGR3).jmp – repeat for relapses 2-9

*: all INEC relapses included

AMS2DT: Time to start of alternate treatment including β -interferon

Table 51: Reviewer table extracted from Sponsor CSR Table 149 – ARR by subgroups

	150 mg DAC HYP			30 ug Avonex		
	Region 1 N=118	Region 2 N=210	Region 3 N=591	Region 1 N=118	Region 2 N=207	Region 3 N=597
ARR adjusted	0.227	0.227	0.212	0.321	0.498	0.374
95% CI	0.162, 0.320	0.173, 0.299	0.182, 0.246	0.233, 0.442	0.395, 0.629	0.327, 0.428
Rate ratio (DAC HYP/Avonex)				0.709	0.456	0.566
95% CI				0.458, 1.098	0.326, 0.637	0.463, 0.690
p-value				0.1191	<0.0001	<0.0001

Source: Study 301 CSR Table 149 page 864/3937

Reviewer Comment: The apparent smaller treatment effect in Region 1 may be attributable to the small sample size and wide confidence interval for this Region. It may also reflect the higher

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proportion of subjects who had been treated previously for MS, i.e. a more refractory population compared to the other regions. The point estimate in Region 1 nevertheless favors DAC HYP.

Sex

The ARR was similar for males and females with a relative reduction of 35.3% for females and 46.6% for males.

Table 52: Reviewer table: unadjusted ARR by Sex and planned treatment in period one, ITT

	150 mg DAC HYP		30 ug Avonex	
	Females	Males	Females	Males
INEC confirmed relapses	299	125	446	221
Sum(Days to AMS2DT else Days on Study in Period One plus 1	484826	233409	467539	219942
ARR	0.225	0.196	0.348	0.367
Treatment difference			0.123	0.171
Relative reduction in ARR			35.3%	46.6%

Source:Join Study 301 ADSL for ARR with Yes subset of INECCONF subset of Study 301RL incl nonmatches.jsp by TRT01P, RLSTRESC and Sex

Source:Study 301 ADSL for ARR Summ Days to AMS2DT else DOS By (TRT01P).jmp
 AMS2DT: Time to start of alternate treatment including β-interferon

Race

Table 53: Reviewer table: unadjusted ARR by Race and planned treatment in period one, ITT

Planned Treatment	Total	Sum of Days to AMS2DT else Days on Study plus 1					
		AMERICAN INDIAN OR ALASKA NATIVE	ASIAN	BLACK OR AFRICAN AMERICAN	NOT REPORTED*	OTHER	WHITE
150 mg DAC HYP	919	-	0.208	0.341	0.206	0.270	0.213
30 ug Avonex	922	-	0.233	0.381	0.288	0.379	0.358
Treatment difference		-	0.025	0.040	0.082	0.109	0.145

Source: Join Study 301 ADSL for ARR with Yes subset of INECCONF subset of Study 301RL incl nonmatches (by Race).jmp

Source: Study 301 ADSL for ARR By (TRT01P and RACE).jmp

*: Due To Confidentiality Regulations

AMS2DT: Time to start of alternate treatment including β-interferon

Disease Activity

Number of relapses in the past year

Table 54: Reviewer Table: Unadjusted ARR by the number of relapses in the year prior to enrollment group (≤1 vs. ≥2), by planned treatment, ITT

		150 mg DAC HYP	30 ug Avonex
		RL in year prior to enrollment	RL in year prior to enrollment

	Total	N(<=1)	N(>=2)	N(<=1)	N(>=2)
Number of Relapses	1091	205	219	267	400
Unadjusted ARR		0.190	0.247	0.274	0.440
Treatment difference		0.084	0.193		
Relative treatment difference		30.7%	43.9%		

Source: Join Study 301 ADBASE with Yes subset of INECCONF subset of Study 301 RL incl nonmatches.jmp by RL1YGR2 and Join Study 301 ADSL for ARR with ADBASE.jmp by RL1YGR2 (≤ 1 , ≥ 2)

Previous treatment with interferon β

For subjects being treated with DAC HYP the occurrence of relapses was approximately the same for those previously treated compared to those not previously treated with interferon β . For those being treated with Avonex, those previously treated with interferon β had a lower relapse rate than those not previously treated (Table 55).

Table 55: Reviewer Table: Occurrence of INEC- confirmed relapses by treatment group and previous treatment with interferon β

Group ID	Randomization Stratum IFN beta Usage	150 mg DAC HYP		30 ug Avonex		Total Subjects	
		N	% ITT	N	% ITT	N	% ITT
Total Relapses		484	52.7%	731	79.3%	1215	66.0%
	Subtotal N	221	24.0%	415	45.0%	636	34.5%
	Subtotal Y	263	28.6%	316	34.3%	579	31.5%
Total ITT	Subjects	919		922		1841	

Source: JRev CTab RLGRPIDbyTRT01PfilterINECCONF_Y.xls

*: not limited to relapses occurring prior to AMS2DT or prior to end of study.

Reviewer Comment: The proportion of subjects treated with DAC HYP who experienced relapses was similar by previous treatment with an interferon. For those randomized to Avonex the proportion with a relapse was slightly lower for those previously treated with an interferon. These latter subjects do not appear to have been biased toward premature discontinuation of treatment. For the treatment completion rates by treatment assignment see Table 11 and Table 12. Subjects who had been on interferon previously and randomized to interferon for this trial were not any less likely to complete treatment compared to those previously treated and randomized to DAC HYP.

Data Quality and Integrity – Reviewers’ Assessment

The sponsor provided written responses to an FDA comment in the pre-BLA minutes regarding the influence of site financial interests on the study results. Of the 49 sites in the US, 53%

disclosed financial interests as did 15% of the OUS sites. An analysis of adverse event reporting did not reveal any consistent pattern related to financial interests.

Table 56: Reviewer table: ARR for subjects at sites with and without financial interest

ITT	Avonex 922		DAC HYP 150mg 919	
	Number of subjects	% of ITT	Number of subjects	% of ITT
With financial interests	163	18	158	17
Adjusted ARR	0.397		0.184	
(95%CI)	(0.294, 0.537)		(0.129, 0.261)	
Rate ratio			0.462	
(95%CI)			(0.306, 0.698)	
No financial interests	759	82	761	83
Adjusted ARR	0.389		0.221	
(95%CI)	(0.346, 0.437)		(0.193, 0.252)	
Rate ratio			0.567	
(95%CI)			(0.477, 0.674)	

Source: Table 6, Pre-BLA meeting – sponsor written responses, page 212/218

Efficacy Results – Secondary and other relevant endpoints

➤ Number of New or Newly-Enlarging T2 lesions at Week 96

At 96 weeks the number of new or newly enlarging T2 lesions was reduced by approximately 60% (mean reduction -3.62, 95%CI: -4.59, -2.65, p<0.001, unpaired t-test). The table below represents the observed counts without imputation or adjustment for baseline values. The sponsor reports a reduction of 54.4% using a negative binomial regression model with adjustment for baseline volume of T2 lesions, history of baseline use of IFN β and age group. At 24 weeks the reduction was 35.4% (mean reduction -1.4, 95%CI -2.06, -0.74, unpaired t-test).

Table 57: Reviewer table: the number of new or newly enhancing T2 lesions by visit and planned treatment, ITT

Planned Treatment	Visit Name	Number of lesions				
		count subjects	mean	std.dev.	min	max
150 mg DAC HYP	WEEK 24	874	2.55	5.38	0	51
150 mg DAC HYP	WEEK 96	750	2.53	6.71	0	84
30 ug Avonex	WEEK 24	839	3.95	8.23	0	115
30 ug Avonex	WEEK 96	711	6.15	11.61	0	123

Source: JRev IM all T2HPRNE2 by visit and TRT01P.xls

- **Proportion of subjects with sustained disability progression defined by at least a 1.0-point increase on the Expanded Disability Status Scale (EDSS) from baseline EDSS \geq 1.0 that is sustained for 12 weeks or at least a 1.5-point increase on the EDSS from baseline EDSS = 0 that is sustained for 12 weeks**

The week 0 EDSS score was the baseline score for all but 6 subjects. The screening score was used for 5 subjects and the week 12 score for one subject.

The following criteria are of interest for the primary analysis of disability progression:

- The change from baseline EDSS must be 1.5 points or greater for those with a baseline EDSS of 0 and must be 1.0 points or greater for those with a baseline EDSS of greater than 0
- The tentative increase must be confirmed at the next study visit that occurred more than 74 days after the tentative progression.
- Confirmation must occur more than 29 days after the onset of a relapse
- The date of onset of the progression is the date of the onset of the (tentative) progression
- A progression may begin with a relapse
- A progression may not begin after the start of alternative treatment for MS
- A progression may be confirmed after the start of alternative treatment for MS
- For the calculation of the time to sustained progression, those who do not have a progression will be censored at the date of the last valid EDSS determination prior to the end of treatment visit or the date of start of alternative treatment for MS, whichever occurred earlier

See the regulatory history (3.2) regarding the imputation method for those tentative progressions without a confirmatory visit. The primary method assumes that those without a confirmatory EDSS assessment did not progress. Alternative imputation methods including the "multiple imputation" method based on the rate of confirmation for those with a confirmatory EDSS assessment using a logistic model are considered exploratory analyses. The SAP (Section 6.4.1.2) states that a progression must start at or prior to the End of Treatment Period Visit which was the Last Scheduled Treatment Period visit for those who completed treatment. Treatment was allowed for up to 140 weeks.

The sponsor reports that using the primary analysis method there were 121 subjects (13%) treated with DAC HYP 150 mg and 140 subjects (15%) treated with Avonex who met the criteria for 12 week sustained progression of disability by Week 96 of treatment (Study 301 CSR Table 31). Using the Cox proportional hazards model, the hazard ratio for 12 week confirmed progression was 0.84 (95%CI 0.66, 1.07, $p=0.1575$). The sponsor reports that 67 subjects with a tentative progression lacked a confirmatory EDSS, 43 in the Avonex group and 24 in the DAC

HYP group. If these tentative progressions are assumed confirmed, as opposed to not confirmed in the primary analysis method, then the hazard ratio reported by the sponsor becomes 0.76 (95%CI: 0.61, 0.95; p=0.0157). If the confirmation rate for the treatment group is imputed for those lacking a confirmatory EDSS then the hazard ratio becomes 0.786 (95%CI: 0.620, 0.997; p=0.0469). See Study 301 CSR Table 33, page 189/3937. Six month confirmed progression was found in 99 (11%) subjects treated with Avonex and in 80 (9%) subjects treated with DAC HYP. In this analysis the confirmatory EDSS score was imputed for 67 subjects in the Avonex group and for 41 subjects in the DAC HYP group. Assuming that tentative progressions lacking the 6 month confirmatory EDSS score were not confirmed, the hazard ratio was 0.79 (95%CI: 0.59, 1.06; p=0.1186). If it assumed that all were confirmed the hazard ratio was 0.70 (95%CI: 0.56, 0.89; p=0.0034) and if the confirmation rate for the treatment group is imputed for those without a confirmatory EDSS then the hazard ratio was 0.73 (95%CI: 0.55, 0.98; p=0.0332).

Reviewer Comment: A large proportion of subjects with a tentative progression did not have a confirmatory EDSS score and the proportion was greater for the group treated with Avonex for both the 3 month and 6 month confirmed analyses. The assumption that those lacking a confirmatory EDSS did not progress would therefore favor the Avonex group. Assuming that they did progress or imputing the rate for the treatment group would favor the DAC HYP group. The most conservative interpretation of these results would therefore be that these subjects did not progress. This was in fact the pre-specified assumption.

Using simplified methods of identifying confirmed progressions the reviewer estimate of the number and proportion of subjects who had a 12 week confirmed progression of disability using the protocol-defined criteria for a tentative progression and for confirmation are in Table 58 below. The proportion of subjects with a confirmed progression is numerically smaller in the group treated with DAC HYP 150 mg but the difference from those treated with Avonex is not statistically significant using a simple Fisher’s exact test (p= 0.3284).

Table 58: Reviewer estimate of proportion with 12 week confirmed progression*

Any confirmed disability increase starting at regular or unscheduled visit *	All subjects		150 mg DAC HYP N=919		30 ug Avonex N=922	
	N	proportion	N	proportion	N	proportion
No	1606	0.872	809	0.880	797	0.864
Yes	235	0.128	110	0.120	125	0.136
Total	1841		919		922	

Source: Join ADES BL with EDSS Wks 12 to 132 with RL1to9 dates with ADSL with2yr ADPROG12WK with RL 1to6 EDSS incl NMs.jmp by Corrected Censors for any 12 week confirmed progression after regular or unscheduled relapse 1 to 5 visit
 *: onset at or prior to Week 96 visit; onset at relapses one to five included; assumption of no progression is confirmatory assessment missing.

The sponsor analysis of the time to first progression endpoint yields a hazard ratio of 0.84 (0.66,

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1.07) that shows no significant difference between the treatment groups ($p=0.1575$) (Study 301 CSR Figure 5). See the Biometrics review by Dr. Ling for the comparable time to first progression analysis (Table 8 in Dr. Ling’s review).

Reviewer Comment: Results using the simple proportion of subjects meeting the criteria for confirmed progression confirm the sponsor’s analysis using a negative binomial model and a time to event analysis, i.e. that there is no statistically significant difference between treatment groups using the pre-specified imputation method. In response to a request for additional information, the sponsor adequately addressed the 9 subjects for whom the censor in ADPROG12WK conflicted with that of the reviewer analysis. The sponsor’s censor and therefore the total number of subjects with confirmed progression appears to be correct. See response in sequence e0059.

Alternate imputation for missing confirmatory EDSS scores

Using the same dataset used to calculate the proportions in Table 58 but assuming that those with a tentative progression at a regular visit but lacking a confirmatory EDSS were in fact confirmed, reviewer analysis of the proportions with a 12 week confirmed progression of disability are shown in Table 59 (for this analysis the reviewer did not assume progression when the confirmatory EDSS was missing after a tentative progression that started at a relapse).

Table 59: Proportion of subjects with 12 week confirmed progression assuming progression following tentative progression at regular visits, ITT

Any confirmed disability increase starting at regular* or unscheduled visit	All subjects		150 mg DAC HYP N=919		30 ug Avonex N=922	
	N	proportion	N	proportion	N	proportion
No	1560	0.847	788	0.857	772	0.837
Yes	281	0.153	131	0.143	150	0.163
Total	1841		919		922	

Source: Join ADES BL with EDSS Wks 12 to 132 with RL1to9 dates with ADSL with 2yr ADPROG12WK with RL 1to6 EDSS incl NMs.jmp by Censor for any confirmed on confirmation missing at regular visit to Week 96 or after RL1-5

*: confirmation assumed if missing after regular visits to week 96.

The proportions in Table 59 are not significantly different ($p=0.2436$, Fisher’s exact test).

Reviewer Comment: Reviewer analysis of the raw proportion of subjects with 12 week confirmed progression assuming progression if the confirmatory EDSS was missing (Study 301 CSR Table 106/page 596/3937) shows slightly lower proportions of subjects meeting the criteria for progression compared to the sponsor analysis and a non-significant comparison by treatment group. The sponsor reports a slightly higher proportion for the Avonex group and a statistically significant difference using the Cox proportional hazards model ($p=0.0157$). Note that the absolute number of subjects meeting the criteria for confirmed progression as reported by the

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sponsor, with all of the criteria applied, appear to be correct (see response in sequence e0059). See the Biometrics review by Dr. Ling for confirmation of the result for this endpoint using Kaplan-Meier and Cox proportional hazards model.

Using the sponsor's censor from the dataset ADPROGDO which assigns progression to subjects who either had a confirmed progression and for those with a missing confirmatory assessment after a tentative progression, the proportion with progression was 0.158 (145 progressions) in the DAC HYP group and 0.199 (183 progressions) in the Avonex group ($p= 0.242$, Fisher's exact test).

Influence of the higher number of relapses in the Avonex group on the assessment of 12 week confirmed disability

Tentative progressions and their rate of confirmation at 12 weeks are shown in **Table 60**. Most relapses were associated with an increase in the EDSS score that met the criteria for a tentative increase in disability. Approximately 20% of these tentative disability increases were confirmed 12 weeks later compared to approximately 50% of those that started at a regularly scheduled visit.

Reviewer Comment: A reduction in the relapse rate results in a reduction in disability that would have met the criteria for 12 week confirmed progression for 25% of relapses (reviewer estimate).

Table 60: Reviewer table: Proportion of tentative progressions* that were confirmed, by onset visit, ITT

	DAC HYP 150 mg (N=919)		Avonex (N=922)	
	Tentative progressions* N	Number confirmed N (%)	Tentative progressions N	Number confirmed N, %
Regular visits**	481	256 (53.2)	542	271(50.0)
Relapses***	331	73 (22.1)	489	97 (19.8)

*: includes all tentative progressions regardless of whether it was the first

** : at or prior to week 96 visit

***: includes relapses 1 to 5

Reviewer table: number of first 12 week confirmed progressions* that started at a regular visit

First 12 week confirmed progression started at a regular visit	Total 12 week confirmed progressions	N(150 mg DAC HYP)	N(30 ug Avonex)
		Yes	225
		106 (96%)	119 (95%)

Source: Join ADES BL with EDSS Wks 12 to 132 with RL1to9 dates with ADSL with2yr ADPROG12WK with RL 1to6 EDSS incl NMs By (Did the first progression occur at a regular visit-).jmp

*: includes all tentative progressions regardless of whether it was the first

Reviewer Comment: The above analysis suggests that nearly all first confirmed progressions had started at a regularly scheduled visit and therefore reduction in the number of subjects with confirmed progressions, albeit not statistically superior to Avonex, did not depend on the reduction in the number of relapses.

Reviewer Comment: Treatment with DAC HYP 150 mg does not show a statistically significant difference in the proportion of subjects with 12 week confirmed progression of disability. However the comparator is a product that has been shown to reduce in the same endpoint when compared to placebo⁵. Although not statistically significant using the pre-specified imputation method of assuming no progression if the tentative progression could not be confirmed, imputation of a confirmation or imputation of the rate of confirmation for the treatment group both result in a more significant advantage for DAC HYP 150mg treatment. Because there were more missing values for the group treated with Avonex these imputation methods may favor the DAC HYP group. Assuming no progression therefore is the more conservative assumption. A conservative interpretation of the overall results for reduction of longer term disability progression is that the reduction with DAC HYP treatment is comparable to but not superior to any reduction with Avonex treatment.

⁵ http://www.accessdata.fda.gov/drugsatfda_docs/label/2015/103628s5258lbl.pdf

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Dose/Dose Response

Dose/response was not studied in Study 301

Durability of Response

The durability of the efficacy seen in Study 301 was not studied in Study 302. Study 205MS 303 is an open label extension for subjects who completed Study 301 to the Week 144 visit or to the End of Study Visit at Week 96. All subjects in Study 303 were treated with DAC HYP 150 mg SC q4W. Of the 1000 subjects in this study, 506 had been treated with DAC HYP in Study 301 and 494 had been treated with Avonex. The study is not designed to assess efficacy but will provide additional data on relapse rates and progression of disability. Efficacy results are not available at this time.

Additional Analyses Conducted on the Individual Trial

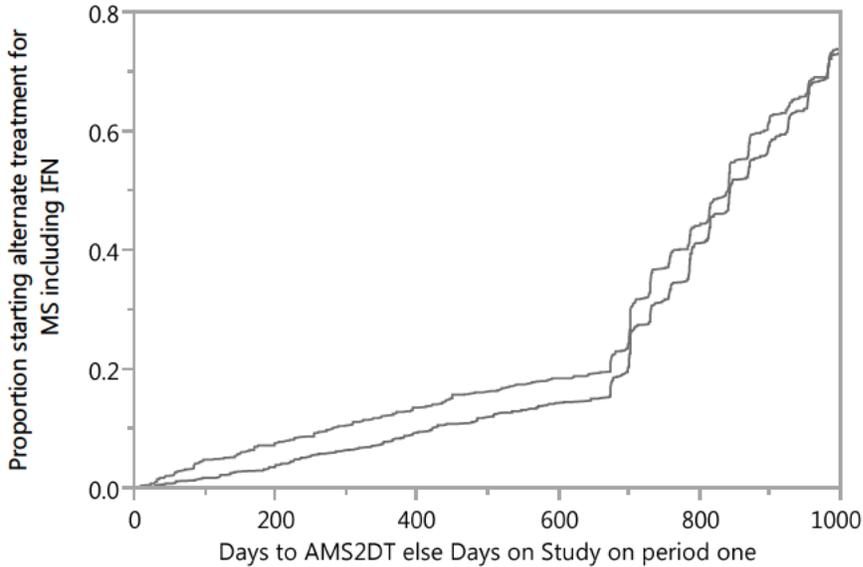
Additional FDA Reviewer Analyses

Time to start of Alternate Treatment for MS (including interferon)

A potential measure of treatment failure may be the choice to start an alternate treatment for MS.

Figure 6: Reviewer Figure: Time to start of alternate treatment for MS including interferon

**Product-Limit Survival Fit
 Failure Plot**



— 150 mg DAC HYP
 — 30 ug Avonex

Time to event: Days to AMS2DT else Days on Study on period one
 Censored by; KM censor for time to AMS2DT
 Censor Code: 1
 Grouped by TRT01P - Planned Treatment for Period 01

Summary

Group	Number failed	Number censored	Mean	Std Error
150 mg DAC HYP	859	60	802.852	8.0793
30 ug Avonex	860	62	767.516	9.29417
Combined	1719	122	785.136	6.17141

Tests Between Groups			
Test	ChiSquare	DF	Prob>ChiSq
Log-Rank	0.9826	1	0.3216
Wilcoxon	3.9606	1	0.0466*

Source: Study 301 ADSL Ir for KM alt trt.jmp

Reviewer Comment: The sponsor provided an exploratory analysis of "Time to Treatment Failure" which was defined as the time to 12 week sustained progression of disability or to start

of alternative treatment or discontinuation of treatment due to lack of efficacy. The hazard ratio for this endpoint was 0.81 (0.65, 0.99; p=0.421) favoring treatment with DAC HYP (Study 301 CSR Table 104, page 591/3937. In response to a request for additional information the sponsor reported 60 and 61 subjects in the DAC HYP and Avonex groups respectively who started alternative treatment for MS during the double blind period of the trial. See response in sequence e0059.

Change from baseline to last recorded EDSS

The sponsor analyzed the change in EDSS score by treatment group at each scheduled time point (Study 301 CSR Section 11.2.4.1.4 and Table 126). At week 96 the mean change from baseline in the group treated with DAC HYP (N=754) was -0.02 and for the Avonex group (N=714) the change was -0.01 (nominal p value = 0.3742). For those subjects with an EDSS score at any given time point the change from baseline is minimal for each treatment group.

Reviewer Comment: The sponsor calculation above excludes subjects who have discontinued prior to week 96. The change from baseline to the last recorded EDSS is shown in the Table 61 below. The difference between treatment with treatment with DAC HYP and Avonex was an increase of 0.11 points. The difference between treatment groups is significant, p=0.0075.

Table 61: Reviewer table: Change in EDSS score from baseline to last recorded EDSS, ITT

Planned treatment in Period 1	Last EDSS change from BL						
	N	Mean	Std Dev	Min	Max	Median	Missing
150 mg DAC HYP	912	0.03	0.84	-3.5	5.5	0	0
30 ug Avonex	907	0.14	0.91	-3	4	0	0

Source: Study 301 Subset of Study 201 301 ADEST1 Ir Chg BL to last EDSS By (TRT01P).jmp and Study 301 Subset of Study 201 301 ADEST1 Ir Chg BL to last EDSS By (TRT01P).jmp

The distribution of the change in last recorded EDSS from baseline is shown in Table 62 below. Relatively few subjects in either treatment group had a decrease in EDSS. Approximately half in each treatment group had no change.

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Table 62: Reviewer table: Distribution of the change from baseline to last EDSS , ITT

Last EDSS change from BL	Total subjects*	N(150 mg DAC HYP)	N(30 ug Avonex)
-3.5	2	2	0
-3	2	0	2
-2.5	8	1	7
-2	18	10	8
-1.5	62	31	31
-1	114	66	48
-0.5	270	146	124
0	828	433	395
0.5	227	103	124
1	123	50	73
1.5	78	33	45
2	50	23	27
2.5	16	5	11
3	5	2	3
3.5	8	3	5
4	7	3	4
5.5	1	1	0
Total	1819	912	907

Source: Study 301 Subset of Study 201 301 ADEST1 Ir - Chg BL to last EDSS By (Last EDSS chg from BL).xlsx
 *22 with missing values.

Table 63: Reviewer table: Last EDSS score to week 96 by treatment group*

TRT01P	N	Last EDSS to Week 96					
		Mean	Std Dev	Min	Max	Median	Missing
150 mg DAC HYP	919	2.48	1.21	0	5.5	2	0
30 ug Avonex	922	2.55	1.26	0	6.5	2.5	0

Source: Join ADES BL with EDSS Wks 12 to 132 with RL1to9 dates with ADSL with2yr ADPROG12WK with RL 1to6 EDSS incl NMs By lastEDSStoWk96.jsp

*: The Week 96 EDSS score was imputed for subjects whose last EDSS score was after Week 96

P-value= 0.2243, unpaired t-test

Reviewer Comment: In response to a request for additional information the sponsor reported the change from baseline to last EDSS to be 2.48 for the DAC HYP group and 2.54 for the Avonex group, confirming the above analysis.

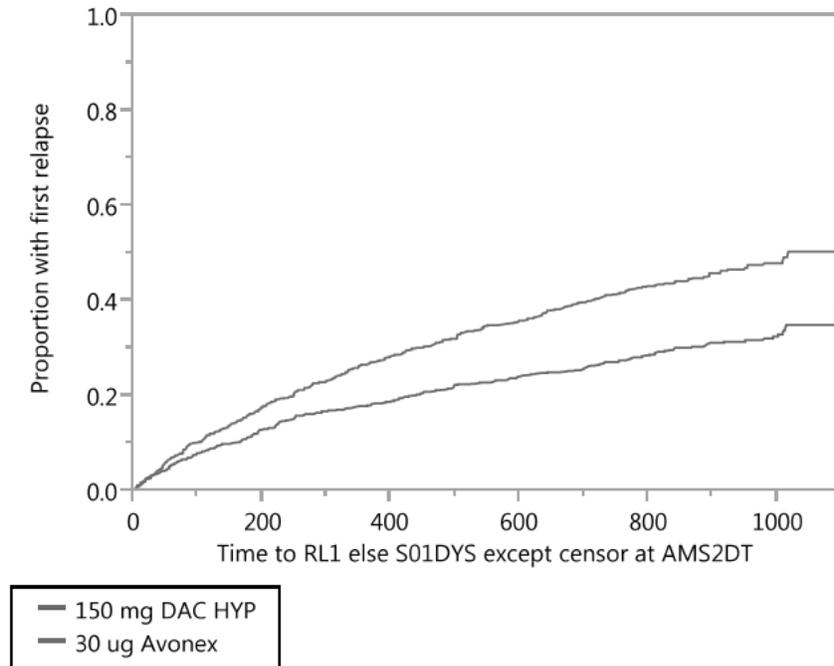
Time to first relapse

The time to first relapse was not a pre-specified endpoint for this trial but is often used as a measure of efficacy. Sponsor analysis of this endpoint showed a difference in favor of DAC HYP 150 mg, nominal p-value <0.001 (Study 301 CSR Figure 6, page 192/3937). A reviewer analysis of this endpoint using the Kaplan-Meier model and censoring at time to end of study or time to the start of alternative treatment (including interferon), whichever came first is displayed in Figure 7 below and does show a significant delay in subjects treated with DAC HYP 150 mg.

Figure 7: Reviewer Figure: Time to first INEC-confirmed relapse, ITT

Product-Limit Survival Fit

Failure Plot



Time to event: Time to RL1 else S01DYS except censor at AMS2DT
Censored by: Censor for INEC confirmed RL 1 using INEC confirmed of Yes
Censor Code: 1
Grouped by: TRT01P - Planned Treatment for Period 01

Summary

Group	Number failed	Number censored	Mean		Std Error
150 mg DAC HYP	259	660	856.399	Biased	12.8929
30 ug Avonex	379	543	709.082	Biased	12.9176
Combined	638	1203	801.488	Biased	9.62469

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Tests Between Groups			
Test	ChiSquare	DF	Prob>ChiSq
Log-Rank	36.1044	1	<.0001*
Wilcoxon	31.3500	1	<.0001*

Source: Join ADSL with Join INED Y RL 1 with RLOSET incl nonmatch.jmp and Time to RL1 using censor INEC_Y and not prior to AMS2DT and AMS2DT else S01DYS.jrp

Change in EDSS at the time of an acute relapse

The change from baseline EDSS to an acute relapse for each relapse up to relapse 6 is shown in Table 64 below. Each relapse is generally associated with an increase of at least one point on the EDSS.

Table 64: Reviewer table: Change from baseline EDSS to EDSS at acute relapse

Treatment	Relapse #	N of Relapses	EDSS change from Baseline		
			Mean	Std Dev	Median
150 mg DAC HYP	1	305	1.11	0.98	1
30 ug Avonex		431	1.07	0.94	1
150 mg DAC HYP	2	119	1.13	1.07	1
30 ug Avonex		200	1.21	1.12	1
150 mg DAC HYP	3	55	1.26	0.94	1.5
30 ug Avonex		84	1.36	1.26	1.5
150 mg DAC HYP	4	23	1.11	1.01	1
30 ug Avonex		33	1.45	1.21	1.5
150 mg DAC HYP	5	10	1.50	1.25	1.25
30 ug Avonex		14	1.18	1.41	0.75
150 mg DAC HYP	6	4	2.25	1.85	2
30 ug Avonex		6	1.25	1.44	1.75

Source: Join ADES BL with EDSS RL1to9 ADSL 2yr ADPROG12WK wRL 1to6 EDSS incl NMs By (TRT01P and EDSSchg RL1).xlsx – tab 2

Reviewer Comment: In response to a request for additional information the sponsor reports a mean change in EDSS at the time of a relapse of 1.28 and 1.36 for the DAC HYP and Avonex groups respectively. An increase of 1.0 point or more was seen in 71% and 73% of the relapses in the DAC HYP and Avonex groups respectively. See response in sequence e0059.

Actual Distance Walked (from EDSS)

EDSS scores up to 5.5 are largely driven by the distance walked. A reviewer analysis of the category for the actual distance walked is shown in Table 65 below.

There is no difference in the proportion of subjects in the Actual Distance Walked categories at Week 0 compared to Week 96.

Table 65: Reviewer Table: Actual Distance Walked at Week 0 and Week 96*

Actual Distance Walked	Total				N(150 mg DAC HYP)				N(30 ug Avonex)			
	Week 0		Week 96		Week 0		Week 96		Week 0		Week 96	
	N	%	N	%	N	%	N	%	N	%	N	%
< 100 M	0	0.0%	33	2.5%	0	0.0%	16	2.4%	0	0.0%	17	2.6%
>= 100 M AND < 200 M	7	0.4%	17	1.3%	1	0.1%	8	1.2%	6	0.7%	9	1.4%
>= 200 M AND < 300 M	82	4.5%	27	2.1%	34	3.7%	11	1.6%	48	5.2%	16	2.5%
>= 300 M AND < 500 M	85	4.6%	57	4.3%	46	5.0%	28	4.2%	39	4.2%	29	4.5%
>= 500 M	1661	90.5%	1180	89.8%	835	91.2%	608	90.6%	826	89.9%	572	89.0%
TOTAL	1835	100.0%	1314	100.0%	916	100.0%	671	100.0%	919	100.0%	643	100.0%

Source: Walk Dis Subset of Week 0 Subset of Join 205MS301 ES with ADSL incl NMs.jmp and Walk Dis Subset of Week 0 Subset of Join 205MS301 ES with ADSL incl NMs.jmp
 *: from EDSS score

Change in Walking Speed

The change in walking speed on the 25 foot Walk Test (25WFT) from baseline to Week 96 for those subjects who had assessments at both visits is in

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Table 66: Reviewer table: Walking speed on 25FWT*, Mean of Trials 1 and 2, change from baseline to Week 96, ITT subjects with assessments at both visits.

Planned Treatment for Period 01	Change from baseline to Week 96 for mean of trials one and two						
	N	Mean	Std Dev	Min	Max	Median	N Missing
150 mg DAC HYP	672	0.58	6.21	-17	96.75	-0.05	247
30 ug Avonex	645	0.65	8.01	-95.05	77.25	0.1	277

Source: Join ADSL with BL and Week 96 trials1and2 incl NMs by Change from BL for mean of trials one and two.jmp

*: Time 25 foot Walking Test

Additional MRI measures of disease activity

Additional imaging endpoints are shown in Table 67 below.

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Table 67: Reviewer table: Summary of key MRI endpoints

MRI endpoint	DAC HYP 150 mg			Avonex			p-value*
	N	Mean	SD	N	Mean	SD	
Week 0							
Total number of T2 hyperintense lesions (T2HPRTOT)	914	48.94	35.4	919	51.82	37.34	0.0904
Total volume of T2 hyperintense lesions (T2HPRVOL)	914	9581	12370	919	10006	11823	0.4522
Total number of T1 hypointense lesions (T1HPOTOT)	914	31.56	33.78	919	34	34.49	0.1262
Total volume of T1 hypointense lesions (T1HPOVOL)	914	3308	5302	919	3477	5388	0.4992
Total number of T1 Gd-enhancing lesions (T1GDTOT)	914	1.96	5.82	919	2.24	5.82	0.3032
Volume T1 enhancing & non enhancing lesions (T1ALLVOL)	914	3288	5368	919	3475	5203	0.4498
Week 96							
New/newly enlarging T2 hyperintense Lesions from previous (T2HPRNE2)	750	2.53	6.71	711	6.15	11.61	<0.0001
Volume new/newly enlarging T2 Lesions from previous visit (T2HPONV2)	750	235	799	711	570	1360	<0.0001
Total volume T2 hyperintense lesions (T2HPRVOL)	750	9070	11329	711	10028	11896	0.1104
Volume of new/newly enlarging T2 lesions compared to previous visit (T2HPONV2)	750	235	799	711	570	1360	<0.0001
Total number of T1-gadolinium enhancing lesions (T1GDTOT)	750	0.33	1.44	711	0.84	2.33	<0.0001
New T1 hypointense lesions from previous visit (T1HPONE)	750	1.06	2.72	711	2.76	6.88	<0.0001
Volume of new T1 lesions fr prev visit (T1HPONV2)	750	56.23	260	711	134.8	346	<0.0001
Total volume of T1 hypointense lesions (T1HPOVOL)	750	3553	5574	711	3793	5594	0.4126
Week 24							
New T1 enhancing & non-enhancing lesions from previous (T1ALLNEW)	874	3.06	3.57	839	4.13	5.63	<0.0001
Volume new T1 enhancing & non-enhancing Lesions from previous (T1ALLNVL)	874	91	188	839	196	493	<0.0001
Volume T1 enhancing & non enhancing lesions (T1ALLVOL)	874	3200	5490	839	3356	5355	0.5523

6.2. **Study 201 - Multicenter, Double-Blind, Placebo-Controlled, Dose-Ranging Study to Determine the Safety and Efficacy of Daclizumab HYP (DAC HYP) as a Monotherapy Treatment in Subjects with Relapsing-Remitting Multiple Sclerosis**

6.2.1. **Study Design**

Overview and Objective

Study 201 was a prospective, randomized, placebo-controlled study in subjects with relapsing MS to compare the effect of two doses of DAC HYP to placebo on the relapse rate and on various imaging surrogate markers after 52 weeks of treatment.

Trial Design

At amendment 4 Study 201 became a randomized, placebo-controlled study of 2 doses of DAC HYP compared to placebo. See earlier versions of the study design under Protocol Amendments below. The protocol planned to enroll 600 subjects randomized 1:1:1 to DAC HYP 150 mg, DAC HYP 300 mg or placebo. Investigational product was to be administered by the treating neurologist or treating nurse in 3 separate subcutaneous doses q4W.

The treatment phase of the study was divided into 3 parts:

Part 1 was a 24-week (weeks 0 to 24) double-blinded, placebo-controlled phase in which subjects were to remain on their assigned treatment. Subjects received investigational treatment as 3 subcutaneous injections q4W for a total of 13 doses.

Part 2 was a 28 week (weeks 24 to 52) double-blinded, placebo controlled phase but beginning at this phase subjects were permitted to start treatment with an interferon approved for the treatment of MS if they had completed Part 1 and a confirmed relapse had occurred.

Part 3 was a 20 week (weeks 52 to 72) double-blinded phase in which subjects were to receive no treatment. Visits occurred q4W.

After Part 2 of the study subjects were eligible to enroll in an open label extension study (205MS202) or to enroll in Part 3.

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The definition of a relapse was the same as in Study 301. The process for identifying and confirming relapses was also the same as for Study 301 (see **Figure 2** in Study 301). As in Study 301 the subject was to contact the treating neurologist within 48 hours of the onset of new symptoms or worsening of existing symptoms. The assessments by the “treating” staff were to be performed within 72 hours of the onset of the potential relapse and the examining neurologist was to perform the EDSS within 5 days of onset. Potential relapses were adjudicated by the “Independent Neurology Evaluation Committee” (INEC). Adjudication was based on clinical data from the treating and examining neurologists and without MRI data.

An EDSS assessment was to be completed every 12 weeks and at unscheduled visits during Parts 1 and 2. An EDSS was also to be completed as part of any potential relapse when the treating neurologist determined that a patient report of new symptoms met the protocol definition of a relapse. All EDSS assessments were to be completed by an “examining neurologist” who was not involved in the care of the subjects and was unaware of other clinical results such as adverse event reports and laboratory results. The (b) (4) score sheet and definitions version 12.05 were used to determine the total EDSS score.

At the end of treatment visit subjects could choose to enter Part 3 of the study or the open label extension study.

Patients were eligible if they were 18 to 55 years old and had a confirmed diagnosis of relapsing MS by McDonald criteria⁵ one through four and had a baseline EDSS of 0 to 5.0. Criteria for disease activity were either 1) 1 relapse in the year prior to randomization with an MRI compatible with MS or 2) the presence of gadolinium-enhancing lesion on a brain MRI performed within 6 weeks prior to randomization. Patients with any progressive form of MS, including secondary progressive MS, were excluded. There were multiple criteria for exclusion based on previous treatment. Female patients were excluded if they were planning a pregnancy during the time that they would be in the study or if they were pregnant or breast-feeding. Male and female patients of child-bearing potential were included only if they agreed to practice effective methods of pregnancy prevention during the trial and for 4 months after the last dose of investigational product.

DAC HYP and matching placebo were administered by the treating neurologist or treating nurse as 3 subcutaneous injections q4W for 48 weeks.

All site personnel were blinded to treatment assignment with the exception of the study Pharmacist.

The systemic use of corticosteroids was not permitted except for the treatment of relapses once the treating and examining neurologists had completed their assessments and it was determined that the relapse met the protocol definition.

Study Endpoints

The primary endpoint was the annualized relapse rate after 52 weeks of treatment.

Secondary endpoints in their order in the closed sequential statistical hierarchy:

1. Reduction in the number of new gadolinium-enhancing lesions over 5 brain MRI scans at weeks 8, 12, 16, 20 and 24 (i.e. in Part 1 of the study) calculated as the sum of the 5 MRI scans. These were done in a subset of the full study population
2. Reduction in the number of new or newly-enlarging T2 hyperintense lesions after 52 weeks of treatment
3. The proportion of subjects who had a relapse between baseline and week 52
4. Change in the MSIS-29 at week 52 compared to baseline.

Reviewer Comment: The effect on reduction of disability was a “tertiary endpoint” (defined as a 1 point or greater increase in EDSS from a baseline of zero or an increase of 1.5 from a baseline of greater than zero - the same criteria as in Study 301).

Statistical Analysis Plan

The sample size was based on the assumption of an ARR of 0.476 in the placebo group (actual rate in the trial was 0.484) and a reduction of 50% reduction in the DAC HYP group. A sample size of 198 subjects per group would provide a 90% power at the 5% type 1 error rate. The sample size estimate included a drop-out rate of 10%.

The primary endpoint was to be calculated using a negative binomial regression model adjusting for the number of relapses in the year prior to enrollment. The same method was used for analysis of the proportion relapsed at 52 weeks (included in the closed sequential testing procedure) and for disability progression (not a specified secondary endpoint). The model included a term for treatment group and baseline value of the respective endpoints. Baseline EDSS (≤ 3.5 vs > 3.5), baseline present/absence of gadolinium-enhancing lesions on MRI and baseline age group (< 40 vs ≥ 40) could be added to the model if found to be a statistical association between any of these three factors and the outcome. The age group category was changed to ≤ 35 vs > 35 – see SAP page 72/284).

To control the type 1 error for multiple comparisons the first comparison was between the DAC HYP 300 mg group and placebo. If this difference was not statistically significant then the comparison to DAC HYP 150 mg would not be considered significant. To control the type 1 error in the analysis of secondary endpoints a closed sequential procedure was used in the rank order above. The first comparison for each secondary endpoint was to be the DAC HYP 300 mg group to placebo followed by the DAC HYP 150 mg group.

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Reviewer Comment: The analysis of progression of disability was not included in the statistical hierarchy and was not adjusted for multiple comparisons.

INEC-confirmed relapses with an onset up to week 52 were included in the ARR. (The last dose of study medication was at week 48 – thus allowing for a 4 week duration of therapeutic drug levels). A relapse with an onset date within less than 30 days of a preceding protocol-defined relapse was considered the same relapse. Relapses that occurred after the start of an alternate treatment for MS were excluded and the time on study was censored at the time of start of the alternative treatment. The start date for this analysis was changed from the date of randomization to the date of the first dose since not all subjects received the first dose on the date of randomization.

The proportion of subjects relapsing was to be based on Kaplan-Meier analysis of the time to first relapse which was based on the date of first dose, date of onset of the first INEC-confirmed relapse or censored at the time of early withdrawal or end of study visit for those who did not have a relapse.

The “additional” endpoint of slowing progression of disability was measured based on either an EDSS increase of 1.5 or more for those with a baseline EDSS of zero or an EDSS increase of 1.0 or more for those with a baseline EDSS of 1.0 or more. Tentative progression had to start prior to the end of week 52. The increase had to be confirmed no less than 12 weeks (minimum 74 days) later. Subjects who met progression criteria were censored at the time of the EDSS score at the start of the progression or, if a confirmed progression did not occur, at the last EDSS assessment. For a tentative progression without a qualifying confirmatory EDSS, censoring was at the last EDSS prior to the tentative progression. Confirmatory visits were allowed up to week 20 of the open label extension or to week 60 for those who did not enter the extension study. A related endpoint of interest is the “change in EDSS” which compared the EDSS at scheduled time points to the baseline EDSS.

The total number of new gadolinium-enhancing lesions was the sum of new lesions at weeks 8, 12, 16, 20 and 24 in the subset with intensive MRI assessments. Missing values were imputed using either the last observation carried forward or the mean number of lesions for the same treatment group. The primary analysis compared the sum of weeks 8 to 24. MRI’s were interpreted by a single independent central reader. In a sensitivity analysis, MRI scans obtained within 24 days of the start of corticosteroid treatment were excluded.

All subjects randomized were included in the primary analysis population.

There was a planned interim futility analysis after 150 subjects completed the Week 24 visit. Futility was to be assessed by the conditional power of the study for both annualized relapse rate and the number of new Gadolinium-enhancing lesions between Weeks 8 to 24.

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The futility analysis was conducted as planned and the study was allowed to proceed. No subsequent adjustment was made to statistical analysis. Global Amendment 6 adding whole brain volume to the tertiary endpoints followed the interim analysis.

Protocol Amendments

The original protocol included 3 DAC HYP doses, 25 mg, 100 mg and 200 mg given SC q4W for 10 doses in addition to a placebo group. At week 20 the placebo group was to start DAC HYP at 100 mg q4W continuing in to “part 2” of the study. “Part 2” of the study was to be a 16 week (weeks 20 to 36) safety extension in which all subjects were to be aware that they were receiving DAC HYP but were blinded to dose. Part 3 was to be a 16 week washout phase in which no study treatment was to be administered.

The original primary objective was to determine the relationship between 3 different doses of DAC HYP on the surrogate endpoint of brain lesion activity as measured by MRI in subjects with relapsing-remitting MS when compared to placebo. The doses chosen for this dose ranging study were based on the results of study DAC-1012 in which a subcutaneous dose of an earlier formulation (Roche Penzberg) at 2mg/kg every 2 weeks was superior to placebo but 1 mg/kg q4W was not. Based on study DAC HYP 1014 in healthy volunteers, the dose of 300 mg q4W would match the high dose exposure in DAC-1012. The dose of 150 mg q4W was expected to be efficacious but “suboptimal”.

Amendment 1, protocol version 2, dated 04May 2006 (the first subject was enrolled on 15February 2008). The following revisions were made:

- Subjects in the placebo group and the DAC HYP 25 mg group were required to remain on the assigned dose until a confirmed relapse occurred, including during weeks 20 to 36 or “Part 2” of the study. Subjects in these two groups would be treated with up to 8 doses of 100 mg DAC HYP if a confirmed relapse occurred before or during Part 2 of the study. Accordingly, Part 2 of the study was no longer considered “a 32-week (Weeks 20 through 52) double-blinded, placebo-controlled extension study in which subjects assigned to placebo or 25 mg DAC HYP will switch to 100 mg DAC HYP q4W after experiencing a confirmed clinical relapse”. Part 3 was revised to include the telephone contact at Week 56 and a single Follow-Up Visit at Week 60.
- The secondary endpoint of the number of T1 hypointense lesions at week 20 was changed to the volume of T1 hypointense lesions at week 20 compared to baseline.
- The change in total lesion volume of new and newly enlarging T2 hyperintense lesions at Week 20 compared to baseline was moved from an additional endpoint to a specified secondary endpoint.

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- The following endpoint was moved to the first of the additional endpoints: the efficacy of DAC HYP in reducing increasing the proportion of relapsing subjects between baseline and end of study

Amendment 2, protocol version 3, 28July 2006

This amendment revised some of the procedures related to the occurrence of fever, infection and injection-site reactions.

Amendment 3, protocol version 4, 16November 2006

- Changed to lowest dose of DAC HYP from 25 mg to 10 mg SC q4W
- Decreased the sample size from 264 to 232.

Amendment 4, protocol version 5, 15June 2007

- DAC HYP doses were changed to 150 mg and 300 mg given as 3 SC injections q4W.
- The number of study subjects and sites were increased
- The objectives were revised. However the primary endpoint remained a surrogate MRI measure, namely the total number of new gadolinium-enhancing lesions over 5 MRI scans at weeks 8, 12, 16, 20 and 24.
- Treatment with interferon- β was allowed after part 1 if a confirmed relapse had occurred
- The duration of parts 1, 2 and 3 were revised. Part 1 was defined as a 24-week (Weeks 0 through 24), double-blinded, placebo-controlled, safety and efficacy treatment phase. Part 2 was defined as a 28-week (Weeks 24 through 52) double-blinded, placebo-controlled extension phase in which subjects were to remain on their assigned treatment. Part 3 was defined as a 20-week (Weeks 52 through 72) double-blinded, follow-up phase in which subjects will not receive study treatment.

Reviewer Comment: The final CSR indicates that enrollment did not begin until Amendment 4. It appears that 155 subjects were enrolled from the start of Amendment 4 to Amendment 5.

Amendment 5, protocol version 6, dated 20 November 2008. The following major revisions were made:

- The primary endpoint was changed to the annualized relapse rate at Week 52. (The first patient had been enrolled on 15 February 2008 and the last subject visit was 30 August 2011).

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- In order to have appropriate power to assess the new primary endpoint the sample size was increased to 198 per treatment group (594 total subjects).
- The method of analysis of the ARR was change from a Poisson regression model to a negative binomial regression model
- Endpoints to assess the effect on progression of disability were added
- The method of determining the proportion of subjects who relapse was changed to Kaplan-Meier survival analysis.
- A futility analysis was added
- The secondary endpoints were place in order of rank for a closed hierarchical approach to multiplicity
- The period between the Screening Visit and the Baseline Visit was changed from 7 days to 21 days.
- Text allowing subjects to participate under “special considerations” was deleted.

Reviewer Comment: Based on the date of consent in the submitted DS dataset, as of 20 November 2008, 155 subjects had been enrolled in the trial prior to the change in the primary endpoint and analysis method.

Protocol version 7, dated 22October, 2010

The following additional objectives were added:

- The efficacy of DAC HYP in reducing brain atrophy on MRI over the 52-week treatment period
- The efficacy of DAC HYP in reducing the total lesion volume of T2 hyperintense lesions over the 52-week treatment period

Data Quality and Integrity: Sponsor's Assurance

Ten sites were audited by the sponsor (sites 454 (21), 559 (13), 110 (6), 505 (25), 507 (8), 752 (11), 758 (21), 903 (21), 301 (10) and 312 (6)). These sites randomized 142 (23%) of the 621 subjects. At each site the scope of these audits included a review of the documentation of the “INV File” and Project Management files, a review of the GCP documentation in the site Investigator File, a review of all Informed Consents for Subjects and SAEs and a review of source documents and CRFs for a sample of subjects. At the Investigator Site, the areas for study conduct, document storage during the study and medication dispensing were observed.

The results of these audits are not provided. However the sponsor reports that site 903 was closed for “misconduct”. The unblinded study pharmacist apparently dosed all 21 subjects from this site with DAC HYP at an unknown dose. This was supported by the PK and PD results.

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Reviewer Comment: The datasets submitted include results for all 621 subjects in this trial. The ITT population however excludes the 21 subjects from this site. These subjects were included in the safety analyses. Sensitivity analyses are provided which include these subjects.

6.2.2. Study Results

Compliance with Good Clinical Practices

In the final Clinical Study Report the sponsor attests that the study was conducted in accordance with Title 21, United States (US) Code of Federal Regulations Parts 50, 54, 56 and 312 Subpart D; the International Conference on Harmonisation (ICH) Guideline on Good Clinical Practice (GCP) (E6); the European Union Clinical Trial Directive 2001/20/EC; and the ethical principles outlined in the Declaration of Helsinki; and/or, where applicable, the European Directive 2001/20 in relation to GCP in the conduct of clinical trials on medicinal products for human use and Directive 2005/28 on GCP for investigational medicinal products (IMPs) for human use.

Financial Disclosure

Both AbbVie and Biogen Idec submitted financial certification and financial disclosure documents for Study 201. For this study there were no sites in the US. A financial interest was disclosed by one or more investigators at 7 of 78 sites (9%), accounting for a total of 60 subjects in the ITT population. A total of \$1.36 million was paid to 15 investigators at 14 sites. These investigators randomized 57 subjects in the study. An analysis of the primary endpoint at sites with and without a financial interest was provided in the written responses to pre-BLA minutes. The ratio of the ARR in the 150 mg group to that in the placebo group was not as favorable at the sites with a financial interest compared to those without. The proportion who met the criteria for progression of disability was lower at sites with a financial interest but the number of such events was too few to influence the overall result.

Patient Disposition

Six hundred and twenty one (621) subjects were screened and informed consent was signed an average of 11±8 days prior to randomization. The protocol required that subjects be screened within 21 days of randomization. Approximately 6% of subjects were screened/consented more than 21 days prior to randomization. The proportion of the latter group is balanced between the treatment groups.

All subjects were from outside the US and Canada.

Table 68: Reviewer table: Number of subjects randomized by country, ITT

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Country	Number of sites	Total randomized
RUSSIAN FEDERATION	14	156
POLAND	11	142
CZECH REPUBLIC	7	94
UKRAINE	12	91
HUNGARY	15	61
UNITED KINGDOM	5	37
INDIA	6	20
GERMANY	6	18
TURKEY	2	2
TOTAL		621

Source: ADSIT201 Ir By (SICNTL).jmp

Over 95% of subjects completed treatment and completed the study. The most common reasons for withdrawal from treatment were withdrawal of consent and an adverse event. Adverse events causing discontinuation of treatment were slightly more common in the two DAC HYP groups. Over 80% of subjects in each treatment group chose to enter the open label study (205MS202) after completing Part 2 and therefore Part 3 of the study had relatively few subjects and was not informative.

Reviewer Comment: See the Review by Dr. Villalba for the types of adverse events that caused discontinuation.

Table 69: Reviewer table: Disposition for Parts 1 and 2 by End of treatment and End of Study by Planned Treatment group.

Subcategory for Disposition Event	Reported Term for the Disposition Event	DAC HYP 150 mg	DAC HYP 300 mg	Placebo	Total Subjects
END OF STUDY	Completed	199 (95.67%)	204 (97.61%)	199 (97.55%)	602 (96.94%)
	Other	19 (9.13%)	18 (8.61%)	17 (8.33%)	54 (8.70%)
	Consent Withdrawn	9 (4.33%)	7 (3.35%)	13 (6.37%)	29 (4.67%)
	Adverse Event	4 (1.92%)	3 (1.44%)	1 (0.49%)	8 (1.29%)
	Lost To Follow-Up	3 (1.44%)	0 (0.00%)	0 (0.00%)	3 (0.48%)
	Investigator Decision	0 (0.00%)	1 (0.48%)	0 (0.00%)	1 (0.16%)
	Subject Non-Compliance	0 (0.00%)	2 (0.96%)	1 (0.49%)	3 (0.48%)
END OF TREATMENT	Treatment Completed	197 (94.71%)	201 (96.17%)	198 (97.06%)	596 (95.97%)
	Consent Withdrawn	9 (4.33%)	5 (2.39%)	11 (5.39%)	25 (4.03%)
	Adverse Event	6 (2.88%)	9 (4.31%)	2 (0.98%)	17 (2.74%)
	Other	3 (1.44%)	2 (0.96%)	2 (0.98%)	7 (1.13%)

Subcategory for Disposition Event	Reported Term for the Disposition Event	DAC HYP 150 mg	DAC HYP 300 mg	Placebo	Total Subjects
	Subject Non-Compliance	0 (0.00%)	1 (0.48%)	2 (0.98%)	3 (0.48%)
	Investigator Decision	0 (0.00%)	0 (0.00%)	1 (0.49%)	1 (0.16%)
	Lost To Follow-Up	1 (0.48%)	0 (0.00%)	0 (0.00%)	1 (0.16%)
RECORD OF DEATH	Death	1 (0.48%)	0 (0.00%)	0 (0.00%)	1 (0.16%)
TOTAL*		208 (100.00%)	209 (100.00%)	204 (100.00%)	621 (100.00%)

Source: Study 201 DS DSTERM by DSSCAT filter DSCAT_DispEvent.xls

*: subjects may have had more than one disposition event between the two parts of Study 201

Protocol Violations/Deviations

The number of deviations that were considered major was 148 for the DAC HYP 150 mg group, 136 for the DAC HYP 300 mg group and 111 for the placebo group. The most common major deviation in all treatment groups involved key study procedures, usually a missed or out of window assessment. These were balanced between the treatment groups. There were no deviations from assigned treatment, i.e. all 621 subjects received the treatment to which they were randomized.

Table of Demographic Characteristics

The mean age of the population was 35.7 years with a range of from 18 to 55 years. Sixty-five percent were female and 96.5% Caucasian. Previous medical conditions were infrequent, the most common being depression in 3.7%, chronic gastritis in 2.7% and hypertension in 2.6%. All of these baseline characteristics were adequately balanced between the treatment groups.

Other Baseline Characteristics (e.g., disease characteristics, important concomitant drugs)

The diagnosis of MS was based on McDonald criterion #1 in 78% of the subjects and this was similar across the treatment groups. In the year prior to randomization, one relapse had occurred in 66.8%, two in 26.4% and three in 4%. No relapses had occurred in the previous year in 3.4% (7 subjects) of the DAC HYP 150 mg group which was somewhat more common than the rate of 2% (4 subjects) in the placebo group and 0.5% (1 subject) in the DAC HYP 300 mg group. The mean number of relapses in the year prior to randomization was essentially the same in all three treatment groups at 1.3 relapses. In the three years prior to randomization the mean number of relapses was approximately 2.4 in each group.

The mean EDSS score was approximately 2.75 for each treatment group, i.e. subjects had minimal disability and could walk independently for at least 500 meters (Table 70).

Table 70: Reviewer table: Mean EDSS score at baseline, ITT

Description of Planned Arm	Baseline EDSS score					
	N	Mean	Std Dev	Min	Max	Median
150 mg DAC HYP	208	2.81	1.15	0	5	3
300 mg DAC HYP	209	2.67	1.21	0	5	2.5
Placebo	204	2.73	1.16	0	5	2.5

Source: Join BLflag_Y subset ES with ADSL By (ARM - Description of Planned Arm).jmp

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

The number of days on treatment was close to the expected duration of approximately 365 days and was balanced between the three treatment groups. Since all injections (3 per visit) were administered by site staff at regular visits, compliance was not an issue. At week 0 one subject in each group did not receive any treatment. By week 48 subjects not receiving the planned treatment were 8 of 189 in the DAC HYP group, 6 of 191 in the DAC HYP 300 mg group and 2 of 181 placebo subjects.

Table 71: Reviewer table: Days on treatment by treatment group for the ITT population*

Planned Treatment	Days on Treatment				
	subjects	mean	std.dev.	min	max
150 mg DAC HYP	201	320.47	60.16	1	365
300 mg DAC HYP	203	321.48	61.22	1	351
Placebo	196	322.77	49.85	56	349

Source: Study 201 ADSL Dys On TRT by TRT01P filter ITTFL_Y.xls

*: subjects from site 903 excluded

Concomitant Medications

Paracetamol was the most commonly used concomitant medication both by subject and by number of uses. The use of NSAIDs before and after injection of investigational product was not required or specifically captured. There were no major differences in the use of any of the NSAIDs by treatment group. Corticosteroids were almost always used to treat relapses. At the subject level, corticosteroids were used for the treatment of a relapse in 43 of 208 subjects treated with DAC HYP 150 mg, 46 of 209 subjects treated with DAC HYP 300 mg and 76 of 204 subjects treated with placebo. The use of corticosteroids for the treatment of other conditions was too infrequent to characterize further.

Efficacy Results - Primary Endpoint

The primary endpoint was the annualized relapse rate using a negative binomial regression model. The covariates in the model were the number of relapses in the year prior to

randomization (one or more than one), baseline EDSS (2.5 or less versus more than 2.5) and baseline age (35 or less versus over 35). Only INEC-confirmed relapses were included. Relapses occurring after the start of an alternative treatment for MS were excluded and the time on study was censored at the start of alternate treatment. Treatment with interferon was not considered an alternate treatment if started in Part 2 of the study. The definition of a relapse in Study 201 was the same as for Study 301.

See the review by Dr. Ling for a review of the ARR calculated by the regression method. The unadjusted ARR was defined as the total number of INEC-confirmed relapses per year at one year after start of treatment.

Relapse identification process

As in Study 301, subjects were to contact the site within 48 hours of the onset of symptoms of a possible relapse. The treating neurologist was to evaluate the subject in person within 72 hours of symptom onset. The examining neurologist was to perform a detailed neurologic examination and an EDSS assessment within 5 days of symptom onset. Based on that evaluation and the other elements of the definition the treating neurologist determined whether a relapse had occurred and should be referred to the INEC for confirmation. The event could be treated with intravenous methylprednisolone without INEC confirmation.

Although the protocol called for prompt evaluation of potential relapses following the onset of symptoms, a delay of more than 7 days occurred in 8.4% of subjects in the placebo group and in more than twice that proportion in both groups treated with DAC HYP. The mean time from relapse onset to evaluation was somewhat greater for the DAC HYP 300 mg group, 6.96± 17.34 days compared to 4.73±5.81 days for DAC HYP 150 mg and 4.02± 6.60 days for the placebo group. The proportion of subjects with an interval more than 7 days from relapse onset to evaluation, displayed in Table 72 was much larger in the two groups treated with DAC HYP compared to placebo.

Table 72: Reviewer table: interval greater than 7 days from relapse onset to evaluation by treating neurologist, all potential relapses, full population

Interval > 7 days	Total subjects		150 mg DAC HYP		300 mg DAC HYP		Placebo	
	N	%	N	%	N	%	N	%
Missing	1	0.5%	0	0	1	1.9%	0	0
No	173	86.1%	43	82.7%	43	79.6%	87	91.6%
YES	27	13.4%	9	17.3%	10	18.5%	8	8.4%
Total	201	100.0%	52	100.0%	54	100.0%	95	100.0%

Source: Join (Join SBEVALDT w RLOSET) with ADSL By (Inter over 7).xlsx

Reviewer Comment: In response to a request for additional information the sponsor reports slightly lower proportions of subjects with an interval from onset to evaluation of more than 7 days (see sequence e0059). The impact of including relapses whose onset was well before the time of evaluation is unknown. This happened more often in the groups treated with DAC HYP. The reliability of accurately identifying a relapse may be compromised by including these relapses. The change in EDSS score compared to baseline may not be representative of the actual change in disability. Whether this would bias the study results in favor of the groups treated with DAC HYP is unknown.

The number of relapses in each treatment group for the ITT is shown in Table 73 below. There were a total of 48 INEC-confirmed relapses in the group treated with DAC HYP 150 mg, 48 in the DAC HYP 300 mg group and 90 in the placebo group.

Table 73: Reviewer table: number of INEC-confirmed relapses by relapse number and treatment group, ITT

RLGRPID**	Relapses, N	150 mg DAC HYP N, proportion of ITT		300 mg DAC HYP N, proportion of ITT		Placebo N, proportion of ITT	
		N	proportion	N	proportion	N	proportion
ITT, N	Total	201		203		196	
		N	proportion	N	proportion	N	proportion
Relapse 1	149	41	0.204	39*	0.192	69	0.352
Relapse 2	32	6	0.030	7	0.034	19	0.097
Relapse 3	4	1	0.005	2	0.010	1	0.005
Relapse 4	1	0	0.000	0	0.000	1	0.005
Total	186	48		48			
No Relapse		160	0.791	164	0.808	127	0.648

Source: RLLORRES not N Subset of INECCONF Subset of ITTFL_Y Subset of Join Study 201 RL with ADSL By (RLGRPID).jmp and INEC conf RL by TRTP and RLGRPID.xlsx

*: one relapse #1 in the DAC HYP 300mg group started after the start of alternative treatment (Study 201/454-007) – the number and proportion would be 38 and 0.187 and the total would be 47 and 0.232

** : RLGRPID: Relapse 1= 113.0; Relapse 2=113.1; Relapse 3=113.2; Relapse 4=113.3

Reviewer Comment: The number and proportion of subjects who had one or more relapses in the table above corresponds closely to the number and proportion reported in the CSR, Table 24. The number of subjects with no relapse was not a pre-specified endpoint but does support the primary endpoint analysis.

Based on the number of days on study at week 52 or to the start of alternative treatment for MS, the unadjusted annualized relapse rates are shown in Table 74 below. These correspond to the rates reported by the sponsor.

Table 74: Reviewer table: Unadjusted Annual Relapse rate, reviewer and sponsor calculations, ITT

Planned Treatment	Subjects, N	Subject years	Relapses to Week 52, N	Annual rate	
				Reviewer	Sponsor*
150 mg DAC HYP	201	194	48	0.247	0.222
300 mg DAC HYP	203	197.6	47	0.238	0.238
Placebo	196	190.5	90	0.472	0.462

*: Table 21 of Study 201 CSR

The clinical relevance of reduction in relapse rate was assessed by examining the incidence of relapses reported as an SAE. The proportion of subjects in whom at least one SAE of MS relapse was reported was 3.1% (21 events) for the DAC HYP 150 mg group and 2.9% (20 events) for the DAC HYP 300 mg group compared to 7.1% (59 events) in the placebo group.

The deficit at the time of a relapse was assessed. The mean change in EDSS score at the time of the relapse was also higher for the placebo group (Table 75). The distribution of the change in EDSS score at the time of a relapse is shown in Table 76.

Table 75: Reviewer table: Summary of the change on EDSS score from baseline to unscheduled relapse visits by treatment group

Planned Treatment	EDSS change from baseline at unscheduled visit						
	N	Mean	Std Dev	Min	Max	Median	N Missing
150 mg DAC HYP	45	1.03	0.89	-1.5	4	1	0
300 mg DAC HYP	43	1.06	0.88	-1	3.5	1	0
Placebo	86	1.48	1.10	-0.5	6	1.5	0

Source: Join Unsched EDSS and BL EDSS with TRT01P from ADSL By (TRT01P - Planned Treatment).jmp

Table 76: Reviewer Table: Distribution of the change from Baseline EDSS to EDSS at unscheduled (relapse) visits, all unscheduled visits, all randomized

EDSS change from baseline at unscheduled visit	150 mg DAC HYP	300 mg DAC HYP	Placebo
	%	%	%

EDSS change from baseline at unscheduled visit	150 mg DAC HYP	300 mg DAC HYP	Placebo
	%	%	%
-1.5	2.22%	0.00%	0.00%
-1	0.00%	2.33%	0.00%
-0.5	0.00%	0.00%	1.16%
0	8.89%	6.98%	4.65%
0.5	22.22%	30.23%	22.09%
1	40.00%	34.88%	18.60%
1.5	15.56%	6.98%	23.26%
2	2.22%	6.98%	12.79%
2.5	2.22%	4.65%	3.49%
3	4.44%	4.65%	6.98%
3.5	0.00%	2.33%	2.33%
4	2.22%	0.00%	3.49%
6	0.00%	0.00%	1.16%
Total	100.00%	100.00%	100.00%

Source: Join Unsched EDSS and BL EDSS with TRT01P from ADSL By (EDSS chg from BL at unsched visit).jmp and EDSS chg from BL dist by Trt grp.xlsx

Reviewer Comment: The relapses reported for the placebo group were more often reported as serious and were associated with a greater increment in disability. However it is conceivable that the greater time delay in assessing subjects in both groups treated with DAC HYP could have contributed to the lower EDSS scores at the time of the relapse in these subjects.

Data Quality and Integrity - Reviewers' Assessment

Identification of relapses

There is no documentation of subject reports of a possible relapse that were determined to not merit an unscheduled in person relapse assessment. The number of times that a subject contacted the investigator is always the same as the number of evaluations by the treating neurologist and the number of times the treating neurologist suspected a relapse. Any bias in the selection of potential relapses for further evaluation cannot be assessed.

Reviewer Comment: The lack of documentation of all subject reports of a possible relapse, as opposed to those that resulted in an unscheduled visit, is the same as in Study 301.

Influence of financial interest

The sponsor provided written responses to an FDA comment in the pre-BLA minutes regarding the influence of site financial interests on the study results. All sites in Study 201 were outside the US. The ARR was reported by subjects at sites with and without a financial interest and is displayed in below. An analysis of adverse event reporting did not reveal any consistent pattern related to financial interests.

Table 77: Reviewer table: ARR by subjects at sites with and without a financial interest

ITT	Placebo		DAC HYP 150mg		DAC HYP 300 mg	
	196		201		203	
	Number of subjects	% of ITT	Number of subjects	% of ITT	Number of subjects	% of ITT
With financial interests	18	9	19	9	23	11
Adjusted ARR	0.407		0.256		0.176	
(95%CI)	(0.198, 0.834)		(0.116, 0.563)		(0.073, 0.423)	
Rate ratio			0.629		0.432	
(95%CI)			(0.213, 1.858)		(0.138, 1.354)	
No financial interests	178	91	182	91	180	89
Adjusted ARR	0.465		0.206		0.239	
(95%CI)	(0.366, 0.592)		(0.144, 0.294)		0.172, 0.334	
Rate ratio			0.442		0.514	
(95%CI)			(0.288, 0.667)		(0.342, 0.773)	

Source: Pre-BLA meeting sponsor written responses, Table 5, page 211/218

Efficacy Results - Secondary and other relevant endpoints

Reduction in the number of new gadolinium-enhancing lesions over 5 brain MRI scans at weeks 8, 12, 16, 20 and 24 (i.e. in Part 1 of the study) calculated as the sum of the 5 MRI scans. These were done in a subset of the full study population

This endpoint was to be assessed in a subgroup of 307 subjects who had monthly MRI scans from week 4 to week 24. The sum of all new lesions from week 8 to week 24 (5 scans) was compared.

The baseline total number of T1 gadolinium-enhancing lesions was higher in the DAC HYP 150 mg compared to both the DAC HYP 300 mg group and to the placebo group.

Table 78: Reviewer table: Total number of T1 gadolinium enhancing lesions at baseline, MRI subgroup.

Planned Treatment	Number of lesions at baseline					
	N	Mean	Std Dev	Min	Max	Median
150 mg DAC HYP	103	2.13	3.83	0	22	1

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Planned Treatment	Number of lesions at baseline					
	N	Mean	Std Dev	Min	Max	Median
300 mg DAC HYP	105	1.10	2.48	0	17	0
Placebo	105	1.09	2.043	0	12	0

Source: T1GDTOT Subset of MRISUBFL_Y Subset of Join Study 201 IM with ADSL LR By (TRT01P - Planned Treatment).jmp
(ANOVA p=0.012).

Table 79: Reviewer table: T1 gadolinium enhancing lesions by visit, MRI subgroup

Visit Name	Planned Treatment	count subjects	mean	std.dev.	min	max	sum	
WEEK 8	150 mg DAC HYP	100	1.15	4.23	0	31	113	
WEEK 12	150 mg DAC HYP	100	0.69	2.03	0	12	66	
WEEK 16	150 mg DAC HYP	98	0.49	1.52	0	11	46	
WEEK 20	150 mg DAC HYP	96	0.46	1.37	0	10	43	
WEEK 24	150 mg DAC HYP	100	0.38	1.36	0	9	36	
		Mean: 3.17 ± 2.1						304
WEEK 8	300 mg DAC HYP	104	0.35	1.13	0	8	36	
WEEK 12	300 mg DAC HYP	101	0.41	1.07	0	5	40	
WEEK 16	300 mg DAC HYP	100	0.20	0.62	0	4	19	
WEEK 20	300 mg DAC HYP	99	0.31	0.98	0	7	30	
WEEK 24	300 mg DAC HYP	103	0.21	0.54	0	2	20	
		Mean: 1.48 ± 0.868						
WEEK 8	Placebo	103	1.35	3.03	0	26	132	
WEEK 12	Placebo	102	1.32	2.57	0	19	129	
WEEK 16	Placebo	100	1.08	2.10	0	14	104	
WEEK 20	Placebo	101	0.74	1.59	0	9	71	
WEEK 24	Placebo	104	1.12	2.42	0	18	109	
Sum		Mean: 1.86 ± 2.34						

Source: JRev SummRep IM MRI cohort_Y NumRes by Visit and TRT01P filter T1GDNEW.xls

Analysis of the mean for the three groups for the sum of the 5 measurements and for each of the five visits individually suggests a significant difference between the three treatment arms with the exception of week 20. The sum for DAC HYP 150 mg is significantly different from placebo (p<0.0001) but DAC HYP 300mg is not significantly different (p=0.1236).

Analysis by the sponsor using a negative binomial model (which did adjust for the baseline value) and using imputation for missing values resulted in a significant benefit at all weeks for both treatment groups (Study 201 CSR Table 22).

Reviewer Comment: The sponsor's result is reasonable given the significantly higher number of Gadolinium-enhancing lesions in the DAC HYP 150 mg group at baseline.

Reduction in the number of new or newly-enlarging T2 hyperintense lesions after 52 weeks of treatment

The number of T2 hyperintense lesions at baseline was higher for the DAC HYP 150 mg group (ANOVA, $p=0.026$) (Table 80).

Table 80: Reviewer table: Number of T2 hyperintense lesions at baseline, MRI subset

Planned Treatment	Visit Name	Numeric Result Finding in Std Format				
		subjects	mean	std.dev.	min	max
150 mg DAC HYP	WEEK 0	101	44.78	35.77	2	160
300 mg DAC HYP	WEEK 0	103	34.50	28.16	0	137
Placebo	WEEK 0	105	36.93	30.97	0	146

Source: JRevRPT IM MRIsubset T2HYRTOT byTRT01P.xls

The number of T2 hyperintense lesions was reduced at both doses of DAC HYP at both 24 and 52 weeks (Table 81). Using a negative binomial model and adjusting for baseline number of lesions the sponsor reported a significant reduction as well (Study 201 CSR Table 23, page 121).

Table 81: Reviewer table: Number of new or newly enlarging T2 hyperintense lesions at weeks 24 and 52, MRI subset

Visit Name	Planned Treatment	Numeric Result Finding in Std Format					ANOVA*
		subjects	mean	std.dev.	min	max	
WEEK 24	150 mg DAC HYP	100	2.18	4.88	0	25	<0.001
WEEK 24	300 mg DAC HYP	103	1.52	2.95	0	11	
WEEK 24	Placebo	104	4.69	5.98	0	34	
WEEK 52	150 mg DAC HYP	98	2.66	5.67	0	33	<0.001
WEEK 52	300 mg DAC HYP	99	1.82	3.16	0	13	
WEEK 52	Placebo	100	7.97	8.91	0	43	

Source: JRev IM MRISUBFL_Y IMSTRESN by VisTRT01P filt IMTEST_T2HPRNEW.xls

The proportion of subjects who had a relapse between baseline and week 52

The number of subjects who did not have a relapse by week 52 was assessed and is shown in Table 82 below.

Table 82: Reviewer table: Number of subjects who were relapse free, ITT

	150 mg DAC HYP N, proportion of ITT		300 mg DAC HYP N, proportion of ITT		Placebo N, proportion of ITT	
ITT, N	201		203		196	
No Relapse*	153	0.761**	155	0.764***	106	0.541

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Source: RLOORRES not N Subset of INECCONF Subset of ITTFL_Y Subset of Join Study 201 RL with ADSL By (RLGRPID).jmp and INEC conf RL by TRTP and RLGRPID.xlsx

*: one relapse #1 in the DAC HYP 300mg group started after the start of alternative treatment (Study 201/454-007) – the number and proportion would be 38 and 0.187 and the total would be 47 and 0.232

** : p =0.0011 vs placebo; ***: p=0.0004 vs placebo (Fisher’s exact test, 2-tailed p-value)

Change in the MSIS-29 at week 52 compared to baseline.

The change in the MSIS-29 physical score was not statistically significant when comparing the DAC HYP 300 mg group to placebo. The difference for the DAC HYP 150 mg group was therefore considered non-significant per the closed sequential testing procedure.

Additional relevant endpoints

Proportion with 12 week confirmed progression of disability

Progression of disability was an exploratory endpoint. The sponsor reports that 25 subjects (13%) in the placebo group, 11 subjects (5%) in the DAC HYP 150 mg group and 15 (7%) in the DAC HYP 300 mg group met the criteria for progression of disability confirmed for 12 weeks. The hazard ratios estimated by the Cox proportional hazards model were 0.43 (0.21, 0.88, p-value = 0.0211) for DAC HYP 150 mg and 0.57 (0.30, 1.09, p-value=0.0905). Reviewer analysis of this endpoint is in **Table 83** below which shows a similar result.

Table 83: Reviewer table: number of subjects with 12 week confirmed progression by treatment group, onset at scheduled or unscheduled visit, full population

Confirmed progression	Total ITT = 621	DAC HYP 150 mg N = 208	DAC HYP 300 mg N= 209	Placebo N= 204
N	51	11	15	25
Proportion of treatment group	0.081	0.053	0.072	0.123

Source: Final Master Join Week 0 to 72 and unsched with ADSL incl nonmatch By (Final corrected Censor for KM for any 12 week confirmed progression).jmp

Placebo vs DAC HYP 150 mg: p value= 0.0143 (Fisher’s exact test)

Placebo vs DAC HYP 300 mg: p value = 0.0964 (Fisher’s exact test)

Reviewer Comment: The reduction in the proportion of subjects with 12 week confirmed progression at the Week 52 point is nominally significant. The absolute number of progressions is small. The relative reduction at one year was 57% and 42% for the DAC HYP 150 mg and 300 mg respectively.

Dose/Dose Response

Study 201 included two doses of DAC HYP, 150 mg and 300 mg SC q4W. Based on the results of Study DAC-1012 it was concluded that doses lower than 150 mg q4W, i.e. 1 mg/kg SC q4W in Study DAC-1012, were expected to be less effective than the 150mg dose. A fixed dose of 300 mg SC q4W was expected to result in serum concentrations comparable to those achieved in the 2 mg/kg arm of study DAC-1012. The dose of 150 mg SC q4W was considered an intermediate dose. There is no indication of an additional benefit of the 300 mg dose (Table 84).

Table 84: Reviewer table: summary of dose response for selected key clinical and imaging endpoints

Endpoint	DAC HYP 150 mg	DAC HYP 300 mg
ARR	54% reduction at 52 weeks	50% reduction at 52 weeks
Proportion of subjects with a relapse	55% reduction at 52 weeks	51% reduction at 52 weeks
12 week confirmed disability progression	57% reduction at 52 weeks	43% reduction at 52 weeks
New Gd-enhancing lesions	69% reduction in sum of new lesions from Weeks 8 to 24	78% reduction in sum of new lesions from Weeks 8 to 24
Number of New or Newly Enlarging T2 Hyperintense Lesions at Week 52	70 % reduction in lesions at Week 52	79 % reduction in lesions at Week 52

Source: Study 201 CSR

Durability of Response

The length of the study does not allow an assessment of the durability of the effects reported after 52 weeks of treatment.

Additional Analyses Conducted on the Individual Trial

Change in disability based on last EDSS score

The change from baseline EDSS score to the last EDSS score up to week 52 is shown in Table 85.

Table 85: Reviewer table: change from BL to last EDSS score*

Planned treatment	Change from BL to last EDSS to Week 52						
	N	Mean	Std Dev	Min	Max	Median	Missing
150 mg DAC HYP	208	-0.07	0.50	-2	1.5	0	0
300 mg DAC HYP	209	0.07	0.62	-2	3	0	0
Placebo	204	0.12	0.70	-2.5	3.5	0	0

Source: Fjinal Master Join By (ARM and EDSSchng from BL).xlsx

*: last EDSS score to week 52

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The change is significant comparing DAC HYP 150 mg to placebo but DAC HYP 300 mg is not different from placebo. The sponsor reported a similar changes and nominal significance levels Study 201 CSR Table 94, page 366/1641).

Reviewer Comment: Although the change from baseline comparing DAC HYP 150 mg to placebo is statistically significant, the absolute change of -0.07 is well within the known variability of the EDSS scale which of 0.5 points¹ and of uncertain clinical relevance.

7 Integrated Review of Effectiveness

7.1. Assessment of Efficacy Across Trials

7.1.1. Primary Endpoints

The reduction in the annualized relapse rate was the primary endpoint for both Study 201 and Study 301. Efficacy for this endpoint is based primarily on the latter study since a reduction after two years of treatment is generally required to support a clinically relevant and sustained benefit. The comparator in Study 301 was Avonex which has been shown to reduce the ARR by approximately 20%⁶. Treatment with DAC HYP 150 mg reduced the ARR by approximately 45% compared to the active comparator. Since treatment duration in Study 201 was for 52 weeks the reduction in ARR by approximately 50% compared to placebo can be considered supportive of the effect seen in Study 301. The reduction in ARR is generally consistent across demographic subgroups. The reduction was also consistent for subgroups based on disease characteristics at baseline.

7.1.2. Secondary and Other Endpoints

A key measure of a clinically relevant effect on subject function is the reduction in progression of disability after two years of treatment. The difference for this endpoint was not statistically significant in Study 301 when compared to Avonex. The absolute reduction was 2% or 19 fewer subjects with progression of disability out of a population of approximately 900. The change in EDSS from baseline to Week 96 in Study 301 and to Week 52 in Study 201 was minimal and not significantly different for the DAC HYP group compared to Avonex. The actual distance walked also did not appear to change significantly (Table 65). There was no difference in the 25 foot Walk time at Week 96 (Study 301 CSR Table 120, page 630/3937). The change from baseline to Week 96 z-score for the 25 foot Walk time did suggest a significant improvement in the group

⁶ http://www.accessdata.fda.gov/drugsatfda_docs/label/2015/103628s5258lbl.pdf

treated with DAC HYP. In summary, the reduction in long term disability with DAC HYP treatment may be considered approximately equivalent to but not superior to that of Avonex.

In study 201 the reduction in the same endpoint after one year of treatment was nominally significant but not included in the statistical analysis plan and not adjusted for multiplicity and therefore deemed not statistically significant. The treatment duration was too short and sample size too small to draw meaningful conclusions on this endpoint in Study 201. The absolute number of progressions is small. Nevertheless the relative reduction compared to placebo of 57% and 42% for the DAC HYP 150 mg and 300 mg respectively does provide some support for a reduction in disability with DAC HYP treatment.

7.1.3. Subpopulations

The clinical trial data does not raise any concerns regarding the applicability of the efficacy results to any subgroup based on fundamental demographic characteristics of MS patients including age group and sex (with the understanding that most patients with MS are female). Only 12% of the subjects in Study 301 and none of the subjects in Study 201 were from the US or Canada. The completion rate was lower for subjects from the US and Canada (**Table 6**). Fewer subjects from the US and Canada in Study 301 were treatment naïve (**Table 22**) which may have influenced the completion rate (**Table 11** and **Table 12**). However there is no indication that these differences impacted the treatment effect and therefore the results appear to be applicable to the population of MS patients in the US.

7.1.4. Dose and Dose-Response

There is relatively little data on the effect of dose of DAC HYP on efficacy. Study DAC-1012 which used weight-based dosing and was based on surrogate endpoints, was interpreted by the sponsor as suggesting that doses below 1 mg/kg may be ineffective. Study 201 suggested that a fixed dose of 300 mg q4W was no more effective than 150 mg q4W. Therefore the choice of 150 mg q4W as the lowest and most effective dose is reasonable.

7.1.5. Onset, Duration, and Durability of Efficacy Effects

A reduction in the ARR is seen at Week 48 in Study 301 (Study 301 CSR Table 126 and Figure 23, page 697/3937).

7.2. Additional Efficacy Considerations

7.2.1. Considerations on Benefit in the Postmarket Setting

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There are no efficacy issues to be addressed in post-marketing studies.

7.2.2. **Other Relevant Benefits**

The significance of the reduction in various MRI measures of MS disease activity has not been established. The reductions seen with DAC HYP treatment are comparable to those seen with recently approved therapies.

7.3. **Integrated Assessment of Effectiveness**

Efficacy is based primarily on the results of Study 301 with supportive evidence from Study 201. The primary endpoint of a reduction in the ARR was met in both studies. The results are consistent across relevant subgroups. Although representation of US subjects is low there are no data to suggest that the overall study results are not applicable to MS patients in the US. The 45% reduction in comparison to an approved treatment for MS is indicative of a clinically relevant reduction in the occurrence of relapses.

The reduction in disability with DAC HYP treatment was not statistically significant in either study. The absolute differences in comparison to either placebo or Avonex in the number and proportion of subjects with disability progression confirmed over 12 or 24 weeks are small. Study 301 did not include a placebo comparator that might provide concurrent evidence for an effect of Avonex on disability. Therefore the results do not provide strong evidence of an effect of DAC HYP treatment on long term disability.

The improvement in various MRI measures of disease activity does not have a well-established relationship to clinical measures of the disease. Although these measures uniformly show a benefit from treatment with DAC HYP they are not an important measure in assessing risk versus benefit.

8 Review of Safety

See the review by Dr. Villalba

9 Advisory Committee Meeting and Other External Consultations

The need for an advisory committee meeting had not been determined at the time of this review.

10 Labeling Recommendations

10.1. Prescribing Information

Prescribing information had not been completed at the time of this review.

10.2. Patient Labeling

Final patient labeling had not been completed at the time of this review

10.3. Nonprescription Labeling

Not applicable

11 Risk Evaluation and Mitigation Strategies (REMS)

The need for a REMS has not been determined at the time of this review

11.1. Safety Issue(s) that Warrant Consideration of a REMS

See the review by Dr. Villalba for safety issues that might merit a REMS.

11.2. Conditions of Use to Address Safety Issue(s)

11.3. Recommendations on REMS

The need for a REMS has not been determined at the time of this review

12 Postmarketing Requirements and Commitments

The need for post-marketing requirements or commitments has not been determined at the

time of this review.

13 Appendices

13.1. References

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13.2. Financial Disclosure

APPEARS THIS WAY ON ORIGINAL

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Covered Clinical Study: Study 205MS201 and 205MS301

Was a list of clinical investigators provided:	Yes <input checked="" type="checkbox"/>	No <input type="checkbox"/> (Request list from Applicant)
Total number of investigators identified: <u>Study 201 - 15; Study 301 - 95</u>		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): <u>0</u>		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): <u>Study 201 - 11; Study 301 - 6</u>		
<p>If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)):</p> <p>Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: <u>0</u></p> <p>Significant payments of other sorts: <u>Study 201 - 15; Study 301 - 6</u></p> <p>Proprietary interest in the product tested held by investigator: <u>0</u></p> <p>Significant equity interest held by investigator in S</p> <p>Sponsor of covered study: <u>0</u></p>		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes <input checked="" type="checkbox"/>	No <input type="checkbox"/> (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes <input checked="" type="checkbox"/>	No <input type="checkbox"/> (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) <u>Study 201 - 707; Study 301- 2437</u>		
Is an attachment provided with the reason:	Yes <input checked="" type="checkbox"/>	No <input type="checkbox"/> (Request explanation from Applicant)

13.3. Eligibility Criteria

Inclusion Criteria

- Ability to understand the purpose and risks of the study and provide signed and dated informed consent and authorization to use protected health information (PHI) in accordance with national and local subject privacy regulations.
- Must be 18 to 55 years of age, inclusive, at the time of consent.
- Must have a confirmed diagnosis of RRMS according to McDonald criteria, numbers 1 through 4 (Polman et al 2005) and a cranial MRI demonstrating lesion(s) consistent with MS (it is not necessary to obtain a current scan if a scan performed previously is available; if a previous scan is not available, then the baseline scan may be used).
- Must have a baseline EDSS between 0.0 and 5.0, inclusive.
- Must meet one of the following disease activity-related criteria:
 - Two or more clinical relapses within the previous 3 years with at least 1 clinical relapse in the 12 months prior to randomization.
 - One or more clinical relapses and 1 or more new MRI lesions (Gd+ and/or T2 hyperintense lesion) within the previous 2 years with at least one of these events in the 12 months prior to randomization. The new MRI lesion must be distinct from one associated with the clinical relapse. The baseline MRI may be used to satisfy this criterion.

Note: For inclusion purposes, a clinical relapse is defined as neurologic signs and/or symptoms documented in the medical record of at least 24 hours duration that are determined by the Investigator or the Treating Neurologist as consistent with an MS relapse. Time since relapse should be measured from the time of relapse onset. When inclusion is based on a new MRI lesion, activity must be verified by the central MRI reading center.

- Women of childbearing potential must be willing to practice effective contraception during the study and be willing and able to continue contraception for 4 months after their last dose of study treatment.

Exclusion Criteria

Exclusions based on medical history

Clinical Review

Lawrence Rodichok MD

BLA 761029

Zinbryta/Daclizumab High Yield Process/DAC HYP

- Diagnosis of primary progressive, secondary progressive, or progressive relapsing MS (as defined by Lublin and Reingold, 1996). These conditions require the presence of continuous clinical disease worsening over a period of at least 3 months. Patients with these conditions may also have superimposed relapses, but are distinguished from relapsing remitting patients by the lack of clinically stable periods or clinical improvement.
- Known intolerance, contraindication to, or history of non-compliance with Avonex 30 mcg.
Note: Current or prior use of an approved IFN β preparation for MS, including Avonex, is allowed, as long as the subject is currently appropriate for Avonex treatment according to local prescribing information.
- History of malignancy; however, subjects with a history of excised or treated basal cell carcinoma or fewer than 3 squamous cell carcinomas are eligible to participate in this study.
- History of severe allergic or anaphylactic reactions.
- Known hypersensitivity to study drugs or their excipients.
- History of abnormal laboratory results that, in the opinion of the Investigator, are indicative of any significant cardiac, endocrine, hematological, hepatic, immunologic, metabolic, urologic, pulmonary, gastrointestinal, dermatologic, psychiatric, renal, neurological (other than MS), and/or other major disease that would preclude administration of DAC HYP or Avonex.
- History of human immunodeficiency virus (HIV) or other immunodeficient conditions.
- History of drug or alcohol abuse (as defined by the Investigator) within the 2 years prior to randomization.
- History of seizure disorder or unexplained blackouts OR history of a seizure within 6 months prior to Baseline.
- History of suicidal ideation or an episode of clinically severe depression (as determined by the Investigator) within 3 months prior to Day 1. Subjects receiving ongoing antidepressant therapy will not be excluded from the study unless the medication has been increased within the 6 months prior to Baseline.
- An MS relapse that has occurred within the 50 days prior to randomization AND/OR the subject has not stabilized from a previous relapse prior to randomization.
- Known history of, or positive screening test result for hepatitis C virus or hepatitis B virus.
- Varicella or herpes zoster virus infection or any severe viral infection within 6 weeks before screening.

- Exposure to varicella zoster virus within 21 days before screening.
- Any of the following abnormal blood tests at screening:
 - hemoglobin ≤ 9.0 g/dL
 - platelets $\leq 100 \times 10^9/L$
 - lymphocytes $\leq 1.0 \times 10^9/L$
 - neutrophils $\leq 1.5 \times 10^9/L$
 - alanine aminotransferase/serum glutamate pyruvate transaminase (ALT/SGPT), aspartate aminotransferase/serum glutamic oxaloacetic transaminase (AST/SGOT), or gamma-glutamyl-transferase ≥ 2 times the upper limit of normal (ULN)
 - serum creatinine \geq ULN.

Exclusions based on Treatment History

- Any previous treatment with daclizumab or other anti-CD25 monoclonal antibody.
- Any type of live virus vaccine from 4 weeks before randomization, including but not limited to: measles/mumps/rubella vaccine, varicella zoster virus vaccine, oral polio vaccine, and nasal influenza vaccine.
- Infection (viral, fungal, bacterial) requiring hospitalization or intravenous (IV) antibiotics within 8 weeks before randomization.
- Elective surgery performed from 2 weeks prior to randomization or scheduled through the end of the study.
- Treatment with another investigational drug or approved therapy for investigational use within the 6 months prior to randomization.
- Prior treatment with the any of the following:
 - total lymphoid irradiation
 - cladribine
 - T cell or T cell receptor vaccination
 - any therapeutic monoclonal antibody, except natalizumab
- Prior treatment with mitoxantrone, cyclophosphamide, fingolimod, or natalizumab within 1 year prior to randomization.
- Prior treatment with any of the following medications or procedures within the 6 months prior to randomization:
 - cyclosporine
 - azathioprine
 - methotrexate
 - mycophenolate mofetil
 - intravenous immunoglobulin
 - plasmapheresis or cytapheresis.

- Treatment with any of the following medications within the 30 days prior to randomization:
 - IV corticosteroid treatment
 - oral corticosteroid treatment
 - glatiramer acetate

Note: Subjects who are currently receiving an approved IFN β preparation are not required to washout from IFN β prior to randomization, but IFN β treatment must be discontinued prior to randomization.

- Initiation of treatment or dose adjustment of commercially available Fampridine-SR within the last 90 days.

Note: Subjects who have been on a stable dose of commercially available Fampridine-SR for longer than 90 days are not excluded. Use of compounded or other formulations of 4-aminopyridine is excluded.

- For subjects currently taking valproic acid, carbamazepine, lamotrigine, or phenytoin:
 - Subjects treated with any of these agents for fewer than 6 months prior to randomization are excluded from study participation unless they discontinue the agent(s) prior to randomization.*
 - Subjects treated with 2 or more of these agents for more than 6 months prior to randomization are excluded from study participation unless they reduce to 1 agent prior to randomization.*
 - Subjects who have had dose escalations of one of these agents within the 6 months prior to randomization are excluded from study participation unless they revert to a previous dose that had been used for at least 6 months prior to randomization or unless they discontinue the agent prior to randomization.*

*Subjects may use an alternative medication allowed by the protocol as needed

Note: Subjects who have been taking 1 of these medications at a stable dose for at least 6 consecutive months prior to randomization may continue to receive the medication without alteration and are eligible for study participation.

- Subjects who are currently receiving treatment with isoniazid, propylthiouracil, or nimesulide at the time of randomization and are not able

to discontinue the agent or change to an alternative medication allowed by the protocol (see Section 11.4) prior to initiation of study treatment.

Miscellaneous exclusion criteria

- Female subjects who are currently pregnant or breastfeeding.
- Female subjects considering becoming pregnant while in the study.
- Previous participation in this study.
- Subjects for whom MRI is contraindicated, i.e., have pacemakers or other contraindicated implanted metal devices, are allergic to gadolinium, or have claustrophobia that cannot be medically managed.
- Unwillingness or inability to comply with the requirements of the protocol, including the presence of any condition (physical, mental, or social) that is likely to affect the subject's ability to comply with the protocol.
- Other medical reasons that, in the opinion of the Investigator and/or Biogen Idec, make the subject unsuitable for enrollment

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/s/

LAWRENCE D RODICHOK
03/10/2016

JOHN R MARLER
05/04/2016

Clinical Review
 Maria Lourdes Villalba, M.D.
 BLA 761029
 Daclizumab High Yield Process (Zinbryta™)

CLINICAL REVIEW

Application Type	Original NME BLA
Application Number(s)	761029
Priority or Standard	Standard
Submit Date(s)	February 27, 2015
Received Date(s)	February 27, 2015
PDUFA Goal Date	May 27, 2016 (extended clock)
Division/Office	DNP/ODEI
Reviewer Name(s)	Maria Lourdes Villalba, M.D.
Review Completion Date	MARCH 23, 2016
Established Name	Daclizumab High Yield Process
(Proposed) Trade Name	Zinbryta™
Applicant	Biogen Idec/AbbVie
Formulation(s)	150 mg/ml injection
Dosing Regimen	150 mg subcutaneously, once a month
Applicant Proposed Indication(s)/Population(s)	Relapsing forms of Multiple Sclerosis, Adult population
Recommendation on Regulatory Action	Based on its safety profile, I recommend a Complete Response.
Recommended Indication(s)/Population(s) (if applicable)	NA

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Glossary

AC	advisory committee
AE	adverse event
APAP	acetaminophen
BLA	biologics license application
BPCA	Best Pharmaceuticals for Children Act
BR	Bilirubin
BRF	Benefit Risk Framework
CBER	Center for Biologics Evaluation and Research
CDER	Center for Drug Evaluation and Research
CDRH	Center for Devices and Radiological Health
CDTL	Cross-Discipline Team Leader
CFR	Code of Federal Regulations
CMC	chemistry, manufacturing, and controls
COSTART	Coding Symbols for Thesaurus of Adverse Reaction Terms
CRF	case report form
CRO	contract research organization
CRT	clinical review template
CSR	clinical study report
CSS	Controlled Substance Staff
DAC or DAC HYP	Daclizumab High Yield Process
DILI	Drug-induced liver injury
DMC	data monitoring committee
ECG	electrocardiogram

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eCTD	electronic common technical document
EDSS	Expanded Disability Status Scale
ETASU	elements to assure safe use
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act of 2007
GCP	good clinical practice
GRMP	good review management practice
ICH	International Conference on Harmonization
IND	Investigational New Drug
IV MP	Intravenous Methylprednisolone
ISE	integrated summary of effectiveness
ISS	integrated summary of safety
ITT	intent to treat
MedDRA	Medical Dictionary for Regulatory Activities
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Event
NDA	new drug application
NME	new molecular entity
OCS	Office of Computational Science
OPQ	Office of Pharmaceutical Quality
OSE	Office of Surveillance and Epidemiology
OSI	Office of Scientific Investigation
PBRER	Periodic Benefit-Risk Evaluation Report
PD	pharmacodynamics
PI	prescribing information
PK	pharmacokinetics
PMC	postmarketing commitment
PMR	postmarketing requirement
PPI	patient package insert
PREA	Pediatric Research Equity Act
PRO	patient reported outcome
PSUR	Periodic Safety Update report
REMS	risk evaluation and mitigation strategy
SAE	serious adverse event
SAP	statistical analysis plan
SOC	standard of care
TEAE	treatment emergent adverse event

1 Executive Summary

1.1. Product Introduction

Daclizumab is a humanized monoclonal antibody (mAb) of the immunoglobulin G1 (IgG1) isotype that binds to CD25, a subunit of the interleukin-2 receptor (IL-2R) in T cells, and modulates T cell signaling. The Applicant's proposed dose regimen and indication is 150 mg SC once a month, for the treatment of relapsing forms of multiple sclerosis (RMS). Daclizumab High Yield Process (DAC HYP) involves a new manufacturing process for daclizumab. Daclizumab Nutley has been previously in the market for a different indication.¹

1.2. Conclusions on the Substantial Evidence of Effectiveness

Please refer to Dr. Rodichok's review of clinical efficacy.

1.3. Benefit-Risk Assessment

The following table includes the risk part of the benefit-risk assessment. For analyses of condition, current treatment options and assessment of benefit, please refer to Dr. Rodichok's review of clinical efficacy

¹ Daclizumab Nutley has been marketed as Zenapax®. See section 3.1 of this review.

	Summary of Safety	
Dimension	Evidence and Uncertainties	Conclusions and Reasons
Risk	<p>The safety database for DAC HYP includes 3 clinical trials in RRMS: Phase 2, 1-year placebo controlled study (201), Phase 3, 3-year active controlled study (301), a Phase 3, 6-month open label study (302) and their extensions. Drug exposure is adequate (N=2236, 5214 PYRs) and reflects the intended population for use. There was no evidence of dose response in study 201, the controlled study that included two doses of DAC HYP. Study 301 included DAC HYP 150 and IFNβ1a (approximately 920 patients per treatment group).</p> <p>Five deaths (0.2%) occurred in DAC HYP-treated patients including 2 DAC HYP-related (1 of autoimmune hepatitis (AIH), 1 of severe eczema complicated with bacteremia, psoas abscess and ischemic colitis) and 3 in which DAC HYP may have played a role (2 of aspiration pneumonia and sepsis in patients with MS progression and 1 of subarachnoid hemorrhage after a fall in a patient diagnosed with lymphoproliferative disorder who was anticoagulated). Five deaths occurred among patients treated with IFNβ1a, none drug-related (3 beyond 1 month after last dose).</p> <p>Drug-induced liver injury (DILI). Serious DILI including 2 with liver failure (including one fatal AIH mentioned above) occurred in at least 21 DAC subjects (0.9%), including 4 Hy's law cases in the Total DAC HYP database. Eleven patients developed immune mediated hepatitis (7 SAE of autoimmune hepatitis and 4 non-SAE of ALT elevation that led to drug withdrawal [2 of whom associated with a</p>	<p>Major and potentially life-threatening safety issues of drug-induced liver injury (DILI), and other serious immune-mediated reactions including cutaneous reactions, enteropathy, lymphadenopathy and other immune mediated conditions, multiorgan hypersensitivity, infections, depression and suicidality, seizures and malignancies occur at the proposed dose of daclizumab. Onset of events was unpredictable, occurred throughout the course of therapy and even after DAC was discontinued, some resolved months after DAC was discontinued, and some required invasive procedures to diagnose and additional immunosuppressive medications to treat.</p> <p>The safety profile of DAC HYP is consistent with known CD25 and Treg deficiency syndromes characterized by enhanced autoimmunity.</p> <p>Labeling would require a boxed warning for immune mediated conditions and DILI, with recommendations for monthly monitoring up</p>

Summary of Safety		
Dimension	Evidence and Uncertainties	Conclusions and Reasons
	<p>cutaneous reaction, one ANA positive and one associated with anti-smooth muscle antibodies and eosinophilia]) in the total DAC HYP database. SAEs of DILI and transaminase elevations occurred more frequently in DAC HYP than in placebo or IFNβ1a in controlled trials. Onset of DILI is unpredictable; it occurs despite monthly monitoring and can be fatal. Whether patients and physicians will adhere to stringent monitoring recommendations once the drug is marketed is uncertain. A pharmacogenomics study conducted by the applicant did not identify a biomarker that can predict patients at risk for serious DILI.</p> <p>Cutaneous reactions. TEAEs in the Skin and subcutaneous disorders SOC occurred in 40 % of DAC-treated patients; 2% had SAE and 4% discontinued drug because of AE. Cutaneous reactions included eczema, dermatitis, psoriasis, drug eruptions, vasculitis and vitiligo. They occurred more frequently in DAC than in control in the controlled trials. In study 301, the rate of cutaneous AE was 37% and 19%, on DAC 150 and IFNβ1a, respectively; SAE were presented by 1.5% and 0.1% of patients, respectively, and AE led to drug withdrawal in 4.7% and 0.8% of patients, respectively. The events ranged from mild to severe and life-threatening reactions, some requiring treatment with topical tacrolimus and or systemic steroids, and some that took months to resolve after discontinuing DAC HYP. The applicant has not evaluated whether a biomarker can predict patients at risk for serious skin reactions.</p>	<p>to 6 months after the last dose of DAC HYP and stopping DAC HYP when appropriate, notwithstanding that these measures may mitigate but not completely eliminate the risk of these reactions. The magnitude of the potential for serious harm after approval is unknown.</p> <p>Warnings for other approved MS drugs include:</p> <p><u>Immune System</u>: Avonex (IFNβ1a) includes autoimmune disorders (with specific mention of idiopathic thrombocytopenia, hyper- and hypothyroidism, and rare cases of autoimmune hepatitis) identified in the postmarketing setting; Lemtrada (alemtuzumab) includes autoimmunity including thyroid in 34%, immune thrombocytopenia in 2%, glomerulonephropathies in 0.3%). Lemtrada has a REMS with ETASU for autoimmune events.</p> <p><u>Hepatic Injury</u>: Tysabri (natalizumab), Avonex and Gilenya (fingolimod): Serious liver injury</p>

	Summary of Safety	
Dimension	Evidence and Uncertainties	Conclusions and Reasons
	<p>Potential Immune mediated adverse reactions occurred in 691 (27%) of patients in the total DAC HYP database (based on a customized MedDRA query). The most common reactions were cutaneous reactions (eczema/dermatitis/ psoriatic conditions) (15%), lymphadenopathy (6%) and enteropathy (1.2%). Other immune mediated reactions included autoimmune hepatitis, sarcoidosis, celiac disease and immune thrombocytopenia, to list events reported in at least 4 patients. Some events presented concurrently or sequentially in the same patient. For instance, one patient presented eczema, drug induced liver injury, pancreatitis and Type 1 diabetes mellitus over a 2 month period. Some patients required invasive procedures and/or additional immunosuppression for the immune condition. Approximately half of the potential immune reactions were unresolved as of December 2015. The rate of immune mediated reactions using the customized MedDRA query approach in study 301 was 32 % on DAC HYP 150 and 12 % on IFNβ1a. At least 12/919 patients (1.3%) underwent invasive diagnostic or treatment procedures in the DAC HYP treatment group (lymph node aspiration or biopsy, colonoscopy, skin biopsy, thymectomy, thyroidectomy, plasmapheresis, liver biopsy), as compared to 1/922 (0.1%) in the IFNβ1a group (thyroid biopsy). The onset of immune mediated reactions is unpredictable. The severity of the event and the work up and treatment required depends on the organ system involved. The applicant has not evaluated whether a biomarker can predict patients at risk for immune mediated reactions.</p>	<p>including liver failure and liver transplant for Tysabri and mention of autoimmune hepatitis for Avonex, identified in postmarketing setting. Aubagio (teriflunomide), boxed warning based on postmarketing experience with leflunomide.</p> <p><u>Cutaneous Reactions</u>: Teriflunomide (because of SJS/TEN with leflunomide)</p> <p><u>Acute Hypersensitivity</u>: Natalizumab, Avonex, Tecfidera, Gilenya.</p> <p><u>Infections</u>: Tysabri, Gilenya, Lemtrada</p> <p><u>Depression and suicide</u>: Avonex</p> <p><u>Seizures</u>: Avonex</p> <p><u>Malignancies</u>: Lemtrada (thyroid cancer, melanoma); Gilenya (basal cell carcinoma and non-Hodgkin’s lymphoma identified during postmarketing).</p>

Clinical Review

Maria Lourdes Villalba, M.D.

BLA 761029

Daclizumab High Yield Process (Zinbryta™)

	Summary of Safety	
Dimension	Evidence and Uncertainties	Conclusions and Reasons
	<p>Multiorgan hypersensitivity. Three patients had adverse reactions consistent with drug reaction with eosinophilia and systemic symptoms (DRESS) and at least 5 others had multiorgan involvement that may have been immune-mediated (including 1 hemophagocytic syndrome, 1 systemic vasculitis and 1 sepsis syndrome).</p> <p>Acute hypersensitivity included urticaria, angioedema and anaphylaxis. Angioedema occurred in 3.6 of all patients exposed to DAC HYP. In study 301, angioedema occurred in 2.4% of patients on DAC HYP and 1.2% on IFNβ1a. Acute hypersensitivity may occur at any time during treatment.</p> <p>Infections. Serious infections occurred in 4.4% of subjects in Total DAC HYP, including 6 cases of sepsis/septic shock (3 complicating aspiration pneumonia and MS progression [2 fatal, mentioned under deaths] and 3 urosepsis) (<i>not including the cases of sepsis syndrome that could be immune mediated</i>). SAEs occurred more frequently in DAC HYP than in control in the controlled trials (4.6% vs 1.6% in study 301) and included bacterial, viral, and mycobacterial infections.</p> <p>Depression and suicidality. SAEs of Depression and Suicide attempt occurred in 0.3% and 0.2% respectively, among DAC HYP treated patients. There was no imbalance in psychiatric SAEs in controlled studies.</p>	<p>Because of the serious safety concerns associated with the use of this biologic agent, I recommend a Complete Response, unless the efficacy is overwhelming.</p>

	Summary of Safety	
Dimension	Evidence and Uncertainties	Conclusions and Reasons
	<p>Seizures. Seizures were reported in 0.9% of patients in the Total DAC HYP database. Seizure SAEs occurred in 0.7% of DAC HYP and 0.2% of IFNβ1a treated patients in Study 301; TEAEs of seizures occurred in 1.2% of DAC subjects and 0.3% of interferon beta-1a subjects. IFNβ1a has a Warning in labeling regarding seizures.</p> <p>Malignancies. Eight women (1 in Study 301 and 7 in extension studies), and 1 man had breast cancer in the total DAC HYP database. Three patients were treated for non-Hodgkin's lymphoma (NHL) and one had a suspected lymphoma that reverted after DAC HYP discontinuation in extension studies. Breast cancer and NHL occurred at rates greater than reported background rates in the general population.</p>	
Risk Management	<p>• If DAC HYP is approved, strong product labeling including a boxed warning for immune-mediated reactions and DILI would be necessary. (b) (4)</p> <p>• Strict eligibility and monitoring in clinical trials did not prevent serious DILI or immune reactions, some of which were life-threatening, required hospitalization or invasive diagnostic procedures beyond blood tests, and additional immunosuppressive therapy such as systemic corticosteroid and azathioprine. The outcome of most of these autoimmune reactions is unknown. Some</p>	<p>If approved, strong labeling and a REMS with ETASU may help mitigate some of the risks associated with DAC HYP. A patient registry and post-marketing requirements may help evaluate and further characterize the main safety risks of DAC HYP in the post-marketing setting. A postmarketing study (ies) should include adequate work up of potential immune mediated conditions as well as calcium and glucose levels. The applicant should conduct studies to identify markers for patients at risk of developing autoimmune</p>

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	Summary of Safety	
Dimension	Evidence and Uncertainties	Conclusions and Reasons
	<p>of them did not resolve after several months or years off-DAC HYP.</p> <ul style="list-style-type: none"> As per discussion at the ROC meeting held on March 7, 2016, if approved, this product should have a Risk Evaluation and Minimization Strategy (REMS) with Elements to assure safe use (ETASU). Postmarketing studies and a Registry could potentially address some of the unanswered questions in this database regarding outcome of autoimmune disorders and how to best manage them as well as identify markers for patients at risk of autoimmune reactions, serious cutaneous reactions and DILI. Postmarketing studies should collect data on calcium and glucose levels which were not routinely collected in the clinical program, except for a small open label study (302). 	<p>disorders, serious cutaneous events and DILI.</p> <p>In my opinion given that DAC HYP would be decreasing the rate of MS relapse at the same time that induces a CD25 deficiency syndrome with potential for uncontrolled autoimmunity, this product deserves extensive discussion at an Advisory Committee meeting before it is marketed to patients with MS.</p>

2 Therapeutic Context

2.1. Analysis of Condition

Multiple sclerosis (MS) is a chronic, autoimmune and neurodegenerative disorder of the central nervous system (CNS), characterized by inflammation, demyelination, and oligodendrocyte and neuronal loss. MS affects an estimated 2.5 million individuals worldwide. For more details please see Dr. Rodichok's clinical review.

2.2. Analysis of Current Treatment Options

Treatment strategies in MS usually involve symptom management and use of disease modifying therapies to reduce the frequency of relapses and to slow the accumulation of disability. Daclizumab HYP has been developed for relapsing forms of MS (the most frequent clinical presentation of the disease). Available treatments are summarized below.

Table 1. Summary of treatment armamentarium relevant to proposed indication

Product (s) Name	Year of Approval	Dosing/route/Administration	Important Safety and Tolerability Issues/ Other comments
Glatiramer (<i>Copaxone</i>)	1996	20 mg/day, SQ qd	Immediate post injection reaction; chest pain; local lipoatrophy & skin necrosis; may interfere with immune system. Contraindicated in patients with known hypersensitivity to glatiramer or mannitol.
Beta interferon 1b (<i>Betaseron</i>)	1993	0.25mg, increase by 0.0625mg q 6 wks. SQ qod	Depression, suicide and psychotic disorders; Liver injury; anaphylaxis and other allergic reactions; congestive heart failure; decreased peripheral blood counts. Autoimmune disorders (including autoimmune hepatitis). Flu-like symptoms. Local injection reaction. Contraindicated in patients with a history of hypersensitivity to IFNβ or any other component of the formulation.
Beta interferon 1b (<i>Extavia</i>)	2009		
Beta interferon 1a (<i>IFNβ1a</i>)	1996	30 µg, increase by 7.5 µg q 3 wks IM q week.	Cardiotoxicity, secondary acute myelogenous leukemia, severe myelosuppression, fetal harm.
Beta interferon 1a (<i>Rebif</i>)	2002	22 or 44 µg, SQ three times/week	
Mitoxantrone (<i>Novantrone</i>)	2000	12mg/m ² IV, q 3 mo	PML and other opportunistic infections; Hypersensitivity reactions; hepatotoxicity. Available through restricted distribution program (TOUCH®). Contraindicated in patients with prior PML and in patients who had hypersensitivity to TYSABRI.
Natalizumab (<i>Tysabri</i>)	2004	300 mg IV over 1 h, q 4 weeks	First dose bradycardia & AV block; Infections including herpes, cryptococcal and PML; Liver injury; Macular edema; PRES; increased BP.
Fingolimod (<i>Gilenya</i>)	2010	0.5 mg, PO qd	Hepatotoxicity, Teratogenicity. Immunosuppression,
Teriflunomide	2012	7 or 14 mg, PO qd	

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(Aubagio)			infections, peripheral neuropathy, skin reactions, increased blood pressure, respiratory effects. Contraindicated in patients with severe hepatic impairment and patients who are pregnant or may become pregnant.
Dimethyl fumarate (Tecfidera)	2013	120 mg for 7 days, PO then 240 mg bid	Lymphopenia; flushing; PML. Contraindicated in patients with mod/severe renal impairment.
Pegylated interferon	2014	125 mcg every 14 days	Hepatic injury, depression and suicide, seizure, anaphylaxis, injection site reactions, congestive heart failure, decreased peripheral blood counts, autoimmune disorders.
Alemtuzumab	2015	2 injections total	Autoimmune diseases (hemolytic anemia, thyroiditis).

Source: individual products labeling.

There are at least 12 different products available for this indication, each one with its own set of safety issues. For additional discussion please see Dr. Rodichok's review of clinical efficacy.

3 Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

Daclizumab High Yield Process (DAC HYP) has never been marketed in the US. However, a formulation of daclizumab using a different manufacturing process (Daclizumab Nutley) has been marketed as Zenapax® for the prevention of transplant rejection.

Zenapax® was withdrawn from the markets (U.S. and worldwide) in 2009. The sponsor submitted an official withdrawal request for Zenapax® (humanized Anti-TAC, Ro24-7375) in March 2012. The product was not withdrawn for safety reasons. As new agents with a less burdensome dosing schedule for the renal transplant indication were available in the market, use of Zenapax® was becoming very small.²

3.2. Summary of Presubmission/Submission Regulatory Activity

On January 4, 2005, AbbVie opened IND 012120 for DAC HYP for the treatment of relapsing forms of MS. An EOP2 meeting was held on September 5, 2008. The DNP reminded AbbVie of the minimum ICH Guidance exposure recommendations for products intended for chronic use. There was agreement that a QTc study was not necessary if analysis from clinical trials did not suggest an effect on the QTc. For discussions other than clinical safety please see Dr. Rodichok's review.

²Dr. Cavaille Coll's memo dated September 16, 2013. Reference ID: 3374033. Withdrawal was effective as of February 14, 2014.

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A Pre-BLA meeting with AbbVie Inc. was held on October 8, 2014. At that time it was agreed that the application would include two controlled trials (205MS201 a one-year trial with approximately 200 patients per group [placebo, DAC HYP 150 mg and DAC HYP 300 mg]) and 205MS301 (a three-year active controlled trial with approximately 900 patients per group [DAC HYP 150 mg and IFNβ1a®]). It was also agreed that

- The integrated analysis of safety (ISS) would be split between Section 2 (2.7.4. Summary of Clinical Safety [SCS] which would include the text) and Section 5 (5.3.5.3 Reports of analyses of data from more than one study, which would include the tables).
- Because of the difference in design and duration, the two controlled trials would not be pooled for analyses in the ISS. In addition to these studies and their extensions, the overall DAC HYP experience would include a multiple dose clinical pharmacology study (study 205MS302).
- The phase 1 clinical pharmacology studies in healthy volunteers would not be pooled as part of the ISS.

AbbVie submitted the BLA on February 27, 2015. On March 24, 2015 DNP requested safety information which had been agreed upon at the pre-BLA meeting but was missing from the original application. This information was submitted on April 2, 2015.

FDA filed the BLA and granted a Standard review on May 18, 2015. The 74-day Filing letter included several requests for information and clarification from various disciplines, including clinical efficacy and safety. Additional requests for information were required throughout the review of this application. Among the multiple responses, the April 2, 2015 submission was considered to be a Major Amendment. Based on this submission, the Review Clock was extended by 3 months (updated PDUFA date May 27, 2016).

In May 2015, AbbVie Inc. transferred ownership of this BLA to Biogen Idec.

The 120 day Safety Update Report was submitted on June 25, 2015

(<\\Cdsub1\evsprod\BLA761029\0021>).

For additional discussion of regulatory interactions please refer to Dr. Rodichok's clinical review.

3.3. Foreign Regulatory Actions and Marketing History

Not Applicable for DAC HYP. A daclizumab Nutley formulation was available in non-US markets but withdrawn in 2009.

4 Significant Issues from Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety

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4.1. **Office of Scientific Investigations (OSI)**

Based on volume of patients, non-completer rate and the rate of major protocol violations, six sites were chosen for inspection. They were all non-US sites (3 in Poland, 2 in Italy and 1 in the Czech Republic). Evaluation by OSI is pending at the time of this review.

4.2. **Product Quality**

Please see CMC review

4.3. **Clinical Microbiology**

Not Applicable.

4.4. **Nonclinical Pharmacology/Toxicology**

Administration of DAC HYP in monkey identified the skin and the CNS as target organs. There was no NOAEL dose for skin lesions. The applicant believes that skin events may be related to the effect of DAC HYP on NK cells and Tregs, both of which are involved in skin conditions such as atopic dermatitis, psoriasis and contact dermatitis. CNS findings were microglial aggregates in brain and spinal cord. The applicant hypothesized that these aggregates might be an indirect effect of increased intrathecal IL-2 and that rather than a neurotoxic effect, this is a pharmacologic effect of DAC HYP of unknown clinical relevance. For additional information please refer to the FDA Nonclinical Pharmacology review.

4.5. **Clinical Pharmacology**

DAC HYP is a humanized monoclonal IgG1 antibody with human constant regions and engineered variable regions composed of human frameworks and murine complementarity determining regions (CDRs). The DAC HYP drug product was used in all the clinical studies in the clinical development program except for the supportive Study DAC-1012, conducted with daclizumab Penzberg. As per the applicant's statement, the proposed commercial formulation is identical to the DAC HYP formulation used in all phase 3 studies. For better understanding of the potential safety issues that might be anticipated with this product, this section summarizes clinical pharmacology results.

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Table 2. Phase 1 Clinical Pharmacology studies in healthy volunteers. DAC HYP. BLA 761029

Trial ID	Trial Design/ duration	Regimen/ schedule/ Route	Patients enrolled (completed)
Single dose			
DAC-1015	DB, PC Single dose	DAC HYP single dose, SC dose escalating	34 (32)
DAC-1018	DB, PC single dose	DAC HYP single dose, IV, dose escalating	31 (30)
205HV102	single blind single dose	DAC HYP 75 mg or 150 mg, SC (Japanese & Caucasian)	56 (56)
Multiple dose			
DAC-1014	R, DB, PC Multiple dose, 16 weeks	DAC HYP, 200 mg q 2 weeks x 9 doses, SC DAC HYP 200 mg loading dose + 100 mg q 2 weeks x 8 doses, SC Placebo q 2 weeks x 9 doses, SC	32 (27)

Endpoint was safety, PK and PD parameters in all four studies; all studies are completed. SC: Subcutaneous. IV: intravenous. Source: Table 1 and 7 of SCS. Safety results from the phase 1 trials are summarized in Section 13 of this review.

The pharmacokinetic characteristics of DAC HYP 150 SC every 4 weeks, as provided by the applicant, are summarized below (FDA review is pending at time of this review).

- DAC HYP is a CD25 receptor modulator; Tmax (Time to maximum concentration) is 1 week
- T_½ (elimination half-life) is 21 days; steady-state at the proposed dose/schedule is achieved in 16 weeks.
- Covariates influencing DAC HYP disposition included body weight (correlating with clearance, and central volume of distribution) and neutralizing antibody (correlating with clearance).
- There is no anticipated drug-drug interaction and no need for dose adjustment based on age, renal or liver function (as per the applicant).

DAC HYP binds to the alpha subunit of the high-affinity interleukin 2 (IL-2) receptor on T cells (CD25), modulating T cell signaling. This binding is hypothesized to reduce MS lesions by inhibition of IL-2 induced cell proliferation and decreased cytokine secretion by activated T cells by down-modulation of CD25 expression on T cells. DAC HYP is associated with reduction of T regulatory cells (Tregs) and expansion of NK cells, among other immunologic effects. Some relevant pharmacodynamic effects are summarized as follows.

- Saturation of CD25 receptors on T-cells was observed within 8 hours of the first SC dosing and was sustained throughout the monthly dosing interval. The mean steady-state trough concentration (approximately 15 µg/mL) exceeded the 5.0 µg/mL concentration required to maintain full saturation of CD25 receptors. Saturation of CD25 resulted on apparent increase in IL-2 levels.

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- Desaturation of CD25 was observed at approximately 16 to 20 weeks in all subjects evaluated after the last 150 mg SC dose at steady state (Study 202).
- DAC HYP treatment resulted in a robust and reversible expansion of CD56^{bright} NK cells as early as 2 weeks after treatment initiation and continued to expand throughout the first 12 to 18 months of treatment, with most of the increase occurring during the first 6 months. During the second year of treatment, the expansion approached a plateau that was sustained for at least 3 years of treatment during continuous dosing.
- DAC HYP induced a decrease in the numbers of CD4+CD127^{low}FoxP3⁺ regulatory T-cells (Tregs) detectable within the first week of treatment initiation. Tregs reached their nadir by approximately Week 8 of treatment, and the number was sustained for at least the next 3 years of continuous dosing.
- After discontinuation of treatment, the number of CD56^{bright} NK cells and Tregs returned to their pretreatment levels within 20 to 24 weeks of the last dose, and unoccupied CD25 receptor levels returned to baseline values by 24 weeks (when DAC HYP serum concentration was ≤ 1 $\mu\text{g/mL}$)
- Within the range of exposures associated with both 150 mg and 300 mg SC every 4 weeks, there was no relationship between DAC HYP exposure and safety or efficacy endpoints.
- DAC HYP clinical trials allowed a missed dose to be taken only within the 2 week period after the scheduled dosing date and otherwise it was skipped and dosing resumed at the next scheduled monthly dosing date. Based on these data, if a dose is missed and it is more than 2 weeks from the missed dose, patients should skip the missed dose, wait to dose again until their next scheduled dose, and then remain on their original monthly dosing schedule. Only one dose should be administered at a time.

As per the applicant, body weight and neutralizing antibody status did not have clinically relevant effects; PK was not influenced by age and there is no anticipated protein binding. (PK/PD was not studied in pediatric or adults >55 years; effects of renal or hepatic impairment were not studied.)

For additional information the reader is referred to the FDA Clinical Pharmacology review. Safety results of Clinical pharmacology studies are discussed in Section 13 of this review (13.3.19), along with safety results from studies conducted with other daclizumab formulations.

Reviewer Comment: Some of the PD effects of daclizumab last 20-24 weeks after drug discontinuation, which supports the use of 6 months (180 days) for cut-off for analyses of AEs, particularly for infections and immune related events.

DAC HYP down-regulates CD25. CD25 deficiency is associated with T cell dysregulation and autoimmunity, similar to the immune dysregulation, polyendocrinopathy, enteropathy, X-linked syndrome (IPEX) caused by mutations of the FOXP3 transcription factor. (3) (43) Moreover,

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human IL2RA null mutation mediates immunodeficiency with lymphoproliferation and autoimmunity (42). For additional discussion see section 8.3 of this review.

4.6. Devices and Companion Diagnostic Issues

DAC HYP was supplied in vials for all clinical studies except for Study 203, where it was supplied in both vials and in Pre Filled Syringe (PFS), and Study 302 and Study 303, where it was supplied in PFS only. The commercial formulation of DAC HYP will be supplied as a PFS for SC delivery.

[REDACTED] (b) (4)
[REDACTED]
[REDACTED]

4.7. Consumer Study Reviews

The proposed labeling provides instructions for self-injecting the product. In clinical studies, DAC HYP was administered by the treating neurologist or nurse at the investigator's office. The applicant submitted a Human Factor study that is being reviewed by DMEPA. The reader is referred to the DMEPA review.

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5 Sources of Clinical Data and Review Strategy

5.1. Table of Clinical Studies

The clinical development program for DAC HYP (also referred to as DAC) consists of seven studies as follows:

- Four Phase 1 clinical pharmacology studies in healthy volunteers (HVs)
- Three clinical trials in subjects with RRMS, two of which had follow up extensions
 - o 205MS201, a phase 2 study has two extensions [205MS202 and 205MS203]
 - o 205MS301, a phase 3 study has one extension [205MS303]
 - o 205MS302, a clinical pharmacology study

An overview of the DAC HYP clinical development program is presented below. Clinical studies are described in Table 3.

Figure 1. Overview of DAC HYP clinical program

Source: Figure 1, SUR submitted 6/25/15.

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Table 3. Summary of studies that contributed to Safety

Trial ID	Trial Design	Regimen/ schedule/ route	Study Endpoints	Treatment Duration	N enrolled (completed)	No. of Countries/ Centers
Completed Controlled Studies to Support Efficacy and Safety						
201 "SELECT"	Phase 2, DB, Pbo C	DAC150; DAC300 or Pbo, q 4 weeks, SC	Efficacy and safety	1 year	621 (577)	9 non-US countries 78 sites*
301 "DECIDE"	Phase 3, DB, active controlled	DAC150 q 4 weeks, SC IFNβ-1a (IFNβ1a) 30 µg Once a week, IM	Efficacy and safety	Up to 3 years	1841 (1418)	29 countries including US & Canada/ 243 sites
Studies to Support Safety						
Completed						
202	Phase 2, DB extension to study 201 (last visit in 201 was baseline visit in 202)	Pbo. Crossed to DAC150 <u>or</u> DAC300 q 4 weeks × 13 doses, SC DAC150 & DAC300_random. to continue q 4 wks × 13 doses, <u>or</u> cross to Pbo q 4 wks × 5 followed by DAC (same dose) × 8 doses, SC	Extended safety including Immunog enicity	1 year	517 (455)	8 non-US countries
Ongoing at time of original BLA submission						
203	Phase 2b, Open label ext. to 202	DAC150 q 4 weeks, SC	Safety	Up to 6.5 years	As of cut-off 1/20/14: 410 (0)	8 non-US countries
303	Phase 3, Open label ext. to 301	DAC150 continue IFN crossed to DAC150 q 4 weeks, SC	safety	Up to 3 years	As of cut-off 2/28/14: 1000 (0)	27 countries including US & Canada
302	Phase 3, Open label, with ext.	DAC150 q 4 weeks x6 doses; Pbo washout 20 weeks, then DAC150	Safety, PK, Immunogeni city	Up to 3 years	As of cut-off 2/3/14, 133	4 countries including US

All in adults with recurrent relapsing forms of multiple sclerosis, included in the ISS as "Total DAC HYP experience." DAC150: DAC HYP 150 mg, DAC300 DAC HYP 300 mg. Source: Applicant's Tabular listing of Clinical Studies. N= number of patients. DB= double-blind. Pbo C= placebo-controlled. Patients from Site 903 were excluded from efficacy analyses but included in safety analyses. As of SUR (with cut-off of November 2014), studies 203 and 302 were completed and study 303 was ongoing. As of SUR (November 2014) 2236 unique patients; 5214 PYRs.

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In addition to the phase 1, 2 and 3 clinical trials with DAC HYP the applicant provided supportive safety data from trials conducted with daclizumab Penzberg and daclizumab Nutley for MS and other indications. Of those, DAC-1012 (a phase 2, dose ranging study of DAC Penzberg in patients with MS who were taking concurrent IFN- β therapy) helped determining the dose to be used in phase 2-3 trials of DAC HYP. Daclizumab Nutley was studied in psoriasis, asthma, uveitis and ulcerative colitis. Although relatively small, these trials used daclizumab for at least 8 weeks, with a 12 week follow up. Safety data from trials with daclizumab Penzberg and daclizumab Nutley is summarized in Section 13 of this review (13.3.19)

Reviewer Comment: Postmarketing safety data exist from daclizumab Nutley (Zenapax®)(which was withdrawn from the market in 2009) and basilixumab (Simulect®)(another anti-CD25 monoclonal antibody currently approved for the prevention of acute renal transplant rejection). Data from these products is briefly discussed also in Section 13 of this review. However, it is important to emphasize that these products were/are used only for a short period (Zenapax was used for up to 5 doses; Simulect is given as 2 doses (one within 2 hours of transplantation surgery and the other 4 days post-transplantation) and that they are part of an immunosuppressive regimen that includes cyclosporine and corticosteroids.

Of note, Studies 203 and 302 each included two substudies, which will not be reviewed in this review (the Autoinjector prototype substudy (reviewed by CDRH) and the Influenza Vaccine, Intensive PK, and Therapeutic protein-drug interaction substudies (reviewed by the Clinical Pharmacology reviewers).

5.2 Review Strategy

This clinical review focuses on the safety profile of DAC HYP. Data sources have been summarized in section 5.1. For efficacy results see Dr. Rodichok's clinical review.

This review follows the format of the CDER Clinical Review Template 2015 Edition, Version date: June 25, 2015.

The clinical protocols for the two controlled studies (205MS201 and 205MS301) are described below, with emphasis on safety-related aspects.

6 Review of Relevant Individual Trials Used to Support Efficacy

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6.1. Study 201

Study 205MS201, also referred to as study 201 or “SELECT” is a multicenter, randomized, double blind, placebo-controlled study of 1-year duration that evaluated the efficacy and safety of DAC in adult patients with RRMS. It started on February 15, 2008 and was completed on August 30, 2011. In general, eligibility criteria were similar to other recently approved immunomodulators for MS. Relevant exclusion criteria are shown in Section 8 of this review.

Eligible subjects reported to the study site to receive study treatment every 4 weeks for 48 weeks (3 subcutaneous [SC] injections) of DAC150, DAC300 or placebo. The doses were chosen based on estimations from a clinical pharmacology study in patients with MS conducted with the Daclizumab Penzberg formulation (DAC 1012, described earlier). Study drug was administered by either the treating neurologist or the treating nurse. Because target drug concentrations were maintained through Week 52, the treatment period comprised Weeks 0 to 52. Patients who completed the study were eligible to continue in an extension study (202); those who did not continue into the extension study were followed until Week 72 (20 weeks, or a total of 180 days after last DAC dose).

Safety assessments: Screening evaluations included routine hematology and blood chemistries, serum pregnancy test, thyroid panel, hepatitis B and C screening, urinalysis, vital signs and ECG. Hematology included hemoglobin, hematocrit, MCV, red blood cell count, white blood cell count (with differential), and platelet count. Blood chemistry: sodium, potassium, chloride, total bilirubin, alkaline phosphatase, ALT/SGPT, AST/SGOT, GGT, blood urea nitrogen, creatinine, and bicarbonate. Hematology and chemistries, pregnancy test and vital signs were done again at baseline and every 4 weeks through Week 40, and at week 52 (or early termination). After baseline, pregnancy tests were done in urine. ECG and urinalyses were repeated at week 24 and 52. Lymphocyte subsets analyses were done in all patients at screening, baseline and every 4 to 8 weeks. Pharmacokinetic and pharmacodynamic assessments were done at screening and selected timepoints during the study, at selected sites.³ Anti-DACab was tested only at baseline and week 24 using ELISA. If Anti-DACAb was positive, neutralizing antibodies were also tested. Local injection site was evaluated before and 30 minutes post dose. Vital signs were measured before dosing and 60 minutes after dosing

³ PK assessments for correlation of trough levels and assessment of potential impact of immunogenic response on drug exposure. PD assessments included The assessment of cell-mediated immunity using Cylex® Immunknow™ assay, assessment of CD25 expression on peripheral T cells, expanded lymphocyte phenotyping addressing T and cluster of differentiation (CD)56+ natural killer (NK) cells. Peripheral blood mononuclear cells (PBMCs) were separated and frozen for further lymphophenotyping and functional analyses. Saved PBMCs could be used for histocompatibility antigen (HLA) phenotype and other functional studies, if needed for correlation of HLA phenotype with any clinical, immunological, or PD observations. Whole blood samples were collected and frozen for possible future ribonucleic acid (RNA) and DNA transcription profiling and genotyping, respectively. Identification and/or analysis of serum biomarkers that may relate to DAC HYP efficacy or MS disease activity such as soluble CD25 level. Serum collected for other assessments could have also been used for biomarker analysis.

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through week 48. Analyses of safety were conducted in the safety population (all subjects who received at least one dose of study treatment).

In order to minimize the risks of MS relapse during placebo use, concomitant use of IFN- β was allowed starting at Month 6 as long as the subject experienced a confirmed relapse.⁴ If the patient had new neurologic symptoms he/she had to contact the treating neurologist/nurse; if the treating neurologist suspected a relapse, an independent neurologist (IN) blinded to study treatment conducted a detailed examination to confirm the relapse. The IN confirmed relapses were used for the primary efficacy analyses. The treating neurologist determined the treatment. Confirmed MS relapses could be treated with intravenous methylprednisolone (IV MP) 1000 mg/day for 3 to 5 days) without discontinuing treatment.

Subjects could be withdrawn from drug treatment because of pregnancy, subject's desire, a medical emergency that required permanent treatment discontinuation and/or unblinding, use of a disallowed concomitant medication without approval from Biogen, accidental unblinding or at the discretion of the investigator for medical reasons or non-compliance. Patients who prematurely discontinued drug treatment and remained in the study for follow-up could receive IVMP as treatment for relapse and alternate treatment for MS if approved by the applicant. They completed a modified schedule of assessments regardless of whether or not they initiated alternative treatment. Follow ups were via telephone, except if a relapse was suspected, in which case the subject needed to return for an unscheduled relapse assessment visit. Subjects could be withdrawn from the study for the same reasons they could stop treatment. Subjects who withdrew from the study needed to complete an Early Termination visit assessment and were no longer followed in the context of the protocol, except in the case of SAE or pregnancy.

Protocol amendments/ Change to planned analyses

The original protocol 201, dated 28 March 2006 included placebo and several DAC doses for 20 weeks with blinded follow up for 40 weeks. Subsequently, after results of DAC-1012 were available but before the first patient was enrolled, the doses for study 201 were determined to be DAC 150mg, 300 mg and placebo. While the trial was ongoing, there were two protocol amendments related to safety. One was the updated list for lymphocyte phenotyping, measurement of CD25 levels and addition of serum collection for further biomarker assessment; the other was the possibility that patients who completed one year of treatment could participate in a study extension (study 202). *None of these amendments affect the conduct or integrity of the trial.* The final protocol (version 7) is dated 22 October 2010.

⁴ A confirmed relapse was defined as a "new or recurrent neurologic symptoms not associated with fever or infection, lasting at least 24 hours, and accompanied by new objective neurological findings upon examination by the examining neurologist." "New or recurrent neurologic symptoms that evolved gradually over months were considered disease progression, not an acute relapse."

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6.2. Study 301

Study 205MS301, also referred to as study 301 or “DECIDE” is a multicenter, randomized double blind active controlled trial of up to 3-years duration conducted to evaluate the efficacy and safety of daclizumab as compared to IFN β 1a in patients with RRMS. It started on May 11, 2010 and was completed on March 5, 2014. Subjects were randomized in a 1:1 ratio to receive DAC150 SC once every 4 weeks (plus IFN β 1a placebo intramuscularly (IM) once weekly) or IFN β 1a 30 μ g IM once weekly (plus DAC placebo once every 4 weeks) for 96 to 144 weeks. The dose of DAC was chosen based on study 1020 and on results of study 201. DAC HYP was administered in the clinic; IFN β 1a was not, except for the first dose.

If a relapse was suspected, the subject was to undergo an Unscheduled Relapse Assessment Visit. In this study, all MS relapses were reported as AEs.

Concomitant medication with any of the following was not allowed during the study:

- Any alternative disease-modifying MS drug or biologic or other immunomodulatory treatments (e.g. IVIG, plasmapheresis) (except for a stable dose of Fampridine-SR started prior to randomization).

- Systemic steroid therapy, including, but not limited to, oral corticosteroids (e.g. Prednisone) or periodic (e.g., monthly) treatment with IVMP, except for protocol-defined treatment of relapses as described below or for limited, acute treatment of general medical conditions.

- Antineoplastic or chemotherapeutic agents

Subjects who experienced a suspected MS relapse could be treated with IV MP 1000 mg/day for 3 to 5 days. Subjects who experienced an Independent Neurology Evaluation Committee- (INEC) confirmed relapse were required to re-consent for continued study participation at the next scheduled study visit.

Safety assessments: Were very similar to study 201 up to week 24 and for Week 144 (or early termination visit). Between Weeks 24 and 144, hematology and blood chemistries were done every 12 weeks until Amendments 1 and 2 (see Amendments below). Anti DAC antibodies were measured more frequently in study 301 than 201. Pregnancy tests were done less often in study 301. Patients who completed the treatment period could enroll in an open label extension (study 303). Reasons for study treatment discontinuation and study discontinuation and procedures after discontinuation were similar to those in study 201. Safety analyses were conducted up to 180 days after last dose.

Protocol Amendments

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The original protocol was dated Nov 9, 2009. The trial started on May 11, 2010. Subsequent to a case of fatal autoimmune hepatitis in study 202, there were 2 safety amendments to protocol 301, involving the evaluation and management of liver and cutaneous events.

Amendment 1, dated **May 27, 2011** (protocol v.2), increased subject monitoring for laboratory signals related to hepatic function to monthly throughout the treatment period, and update criteria for temporary suspension and discontinuation of study treatment for subjects who developed elevations in ALT, AST or total bilirubin. This amendment was implemented in response to the death of a patient from liver failure in study 202, on April 24, 2011, and included the following.

- Study drug should be temporarily suspended if ALT or AST were >3x ULN or Total BR was >2x ULN, or if there was any other clinically significant hepatic test abnormality in the opinion of the investigator. Lab testing needed to be repeated in 1 week to determine if the subject met permanent discontinuation criteria. Drug cannot be reinitiated unless ALT and AST were ≤2xULN, and Total BR ≤ULN (for subjects with established diagnosis of Gilbert's the criterion for BR is >2.5xULN for suspension and <1.5xULN for re-initiation).
- When study treatment is resumed after a temporary suspension, LFTs must be re-evaluated between 2 and 4 weeks after receiving that first dose of study drug and prior to receiving the next dose.
- Study drug must be permanently discontinued immediately if ALT or AST >5x ULN confirmed by an immediate repeat test (preferably within 24 hours). (The previous value for immediate discontinuation was >10xULN.)
- Drug should also be permanently discontinued if
 - o drug was suspended for ≥8 consecutive weeks
 - o drug was already suspended once because of LFT elevation
 - o ALT or AST >3xULN or Total BR >2xULN (>2.5 for Gilbert's) confirmed by tests 1 week apart.
 - o ALT or AST >2x ULN, or total bilirubin >ULN between 2 to 4 weeks after reinitiation of study drug.
- Subjects who must permanently discontinue study treatment due to elevated LFTs would be evaluated for possible toxicological, infectious, immunological, and metabolic causes of liver injury. Unless a cause has been established, a blood sample should be sent to the central lab within one week of drug discontinuation to screen for causes of liver injury. LFT should be followed until resolution is documented.
- The investigator should review and document all concomitant medications and consider discontinuation of all potential hepatotoxic meds. The subject should be referred to a physician with expertise in liver disease.
- LFT monitoring was added every 4 weeks throughout the study until week 140. For those patients not continuing into study 303, LFT continued every 4 weeks until week 24 post-dose (Week 164 of the study). This visit was

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converted into a full safety visit with physical examination, vital signs, 12-lead ECG, blood sample for clinical lab including thyroid function panel, urinalysis and antidrug antibody testing.

Amendment 1 also provided additional guidance to Investigators on the evaluation and management of cutaneous and hematologic events and depression, and removed the need for male contraception. This amendment also increased the sample size from 750 subjects per arm to 900 subjects per arm.

In regards to skin reactions:

- For subjects with a diffuse or severe skin reaction, study treatment must be withheld until event resolution. Patients with clinically significant cutaneous events should be evaluated by a dermatologist. Systemic corticosteroids may be used. The decision to permanently discontinue study treatment should be made by the Principal Investigator in consultation with the dermatologist. However, if an allergic or hypersensitivity reaction to study treatment is suspected, study treatment must be permanently discontinued.

In regards to hematologic tests, upon confirmatory tests 1 week apart, drug should be withheld if WBC count is <2500 cells/ μ L, lymphocyte count is <800 cells/ μ L or platelet count is <75,000 cells/ μ L.

Amendment 2, dated **March 10, 2012** (v.3) included several changes to minimize the possibility of confounding factors for the evaluation of liver and cutaneous toxicity and ensure that the treating neurologist saw the results of liver tests before the next dose. The list of prohibited medication was expanded as follows:

- Regarding new use of valproic acid, carbamazepine, lamotrigine, or phenytoin. Subjects who have been taking one of these medications at a stable dose for at least 6 consecutive months may continue to receive the medication and may continue study treatment under this protocol. However, if any of these medications must be initiated or dose-escalated, study treatment must be permanently discontinued. Subjects treated with any of these medications for fewer than 6 consecutive months, or who take more than 1 of these medications, or who have had dose escalations within the past 6 months must discontinue the medication and use an alternative medication; reduce to ≤ 1 agent that was taken for at least 6 months or permanently discontinue study treatment.
- Regarding use of isoniazid, propylthiouracil (PTU), or nimesulide. Subjects who currently take any of these medications must either change to an alternative medication allowed by the protocol or permanently discontinue study treatment.

The amendment also discouraged the use of herbal or dietary supplements or agents that have established risks of hepatotoxicity or serious rash, added IGE as part of the gamma-globulin

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component of the comprehensive hepatic panel⁵ and clarified that biopsy slides were to be sent to a central dermatology consultant for evaluation.

Reviewer Comment regarding study design of the controlled studies: The eligibility criteria of the clinical studies are appropriate and in general consistent with those of other drugs recently approved for MS from the safety point of view. The criteria for stopping treatment were also appropriate. Of note, study 301 excluded patients with a history of allergic or anaphylactic reactions to any drug. Given the long duration of effects, a cut-off of 180 day after the last dose is appropriate safety analyses.

The placebo-controlled design in study 201 provides valuable information about the background rate of certain events within the target population (e.g. serious infections, transaminase elevation). However, the size of this study (200 patients per group) and duration (only one year) provides limited placebo-controlled and dose-response data for the purpose of evaluation of safety. Study 201 had a protocol definition for MS relapse that involved confirmation by the IEN, however, the protocol did not specifically advise the treating neurologist on when to report a relapse as an adverse event.

The original size of study 301 was 750 patients per arm, which is larger than most MS trials. The protocol was amended to increase the size even further (to 900 patients per arm), which provides a good size active-controlled database for up to 3 years. In study 301 all MS relapses were to be reported as adverse events (as opposed to study 201, in which reporting MS relapse was up to the investigator). This review will not evaluate events of MS relapse.

The selection of IFN beta (specifically IFN β 1a [IFN β 1a], at a standard dose of 30 μ g IM weekly) for this 3 year study is appropriate as IFN β 1a has a well characterized efficacy and safety profile. Of note, IFN β 1a carries WARNINGS for depression and suicide; anaphylaxis and other allergic reactions; decreased peripheral cell lines including rare pancytopenia and thrombocytopenia and rare severe hepatic injury including hepatic failure and asymptomatic transaminase elevation. IFN β 1a also carries PRECAUTIONS for seizures, cardiomyopathy/congestive heart failure and autoimmune disorders (“post-marketing cases of disorders including idiopathic thrombocytopenia, hyper- and hypothyroidism, and autoimmune hepatitis have been reported”). This is a complex trial to conduct. Matching placebo was used for both the once a month subcutaneous DAC HYP dose and the once a week intramuscular

⁵ Full hepatic panel includes: Total protein; antinuclear antibody (ANA); antinuclear antibody pattern; acetaminophen levels; Anti Mitochondrial Antibody (AMA); Anti Smooth Muscle antibody (ASMA); Liver-Kidney Micro-1 Ab IgG; SLA-Ab IgG; Herpes sim virus 2 IgG; Herpes sim virus 1 IgG; HS Vir 1/2 IgM antibody; Cytomegalovirus IgG; Cytomegalovirus IgM; Ceruloplasmin; Ser Electrophoresis; SE albumin; Serum Electrophoresis (SE) Alpha 1, Alpha 2, Beta, Gamma; EBV VCA IgG; EBV VCA IgM; EBV EBNA antibody; HHV-6 DNA PCR; Parvovirus B19 IgG; Parvovirus B19 IgM; VZV ab IgG; VZV ab IgM; Serum Protein Electrophoresis M spike; IgM ab to Hepatitis A virus; Total Ab Hepatitis A virus; HBV DNA PCR Taq Man; HCV RNA Taq 2.0 Exp; Hepatitis E PCR; Hepatitis E Virus IgG; Hepatitis E Virus IgM; Hepatitis B Core Antibody IG; Hepatitis B Core; antibody EIA Hepatitis B Surface Antibody; Hepatitis B Surface Antigen; Hepatitis C virus antibody; Serum IgE; Serum IgG.

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IFNβ1a doses. Patients were to receive NSAID or APAP prophylactic treatment to prevent flu like symptoms with IFNβ1a and IFNβ1a placebo at least for the first 6 months. However, patients are likely to have known if they were on IFN because of the associated flu-like symptoms, particularly if they had a prior exposure to the agent.

Routine evaluations appear adequate in general, except that there was no routine measurement of glucose and calcium levels. For additional comments regarding this issue see Section 8.3., Adequacy of the database.

*There is one important difference in the safety assessments between these two studies. Study 301 and all protocols other than 201, had more stringent eligibility criteria regarding patients at increased risk of liver and cutaneous toxicity (e.g. exclusion of patients taking two potentially hepatotoxic antiepileptic drugs). The original protocols from Weeks 28 to end of study included blood chemistry every 12 weeks. After the **May 2011** amendment blood chemistries were done every 4 weeks including the extension studies. After the **March 2012** amendment liver enzymes needed to be seen by the investigator before the patient was given the next dose.*

As per clarification submitted on 9/25/15 in response to an FDA request, the protocols of all ongoing DAC HYP trials, including extension studies, were amended to have identical liver monitoring requirements, but the timing of when the amendment was implemented at any given site varied by country and other local factors. "Starting in June 2012, sites were provided the option to use a point-of-care analyzer (Trade name Piccolo 510k) for monthly LFT monitoring and, in practice; central labs were obtained every 3 months." For additional comments see Section 8.5 of this review (Specific Safety issues).

7 Integrated Review of Effectiveness

Please see Dr. Rodichok's review.

8 Review of Safety

8.1. Safety Review Approach

My general approach to the evaluation of safety is to review the applicant's results and conduct my own analyses. Some tables presented in this review are reproduced from the applicant's tables but most of the tables I've generated myself or were included in the standard catalog of safety analyses conducted by the JumpStart team (from the Computational Science Center).

The Safety Population was defined as all patients who had received at least one dose of DAC HYP. The safety analyses from phase 2-3 studies in this BLA are presented in three pools as follows

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- Study 201 (1 year placebo-controlled)
- Study 301 (up to 3 years, interferon-controlled)
- Total DAC HYP experience (DAC HYP data from studies 201 and 301 and their extensions (two of which are still ongoing), and one multiple dose clinical pharmacology study (study 302 and its extension)).

Analysis tables for the Total DAC HYP experience in this review refer to the safety population at the time of the 120-day Safety Update Report (SUR) with a cut-off for analyses November 14, 2014. Adverse event tables/analyses presented in this review include data up to 180 days after last dose of study drug including patients receiving alternative MS treatment, unless noted otherwise. Adverse events reported after the cut-off of the SUR are discussed, when applicable (marked with an asterisk (e.g. 301/111-111*)) but are not included in the ISS analysis tables.

My review used the following applications/datasets: For the controlled trials (studies 201 and 301), unless noted otherwise, I used Empirica Study (with technical support from Dr. Ana Szarfman, Office of Translational Science) using the STDM datasets submitted on May 14, 2015. For integrated analyses of safety, I used JUMP of the ADAM datasets submitted with the SUR (June 25, 2015).⁶ Analyses of subpopulations and patient graphic profiles, when included, were generated using either Empirica Study or JReview. For evaluation of selected liver events I used FDA eDISH.

I reviewed narratives and/or sponsor's submitted patient profiles for all cases of deaths, SAE, dropouts due to adverse events and AE of interest. I will present full narratives for all deaths and selected events of interest, and brief narratives or listings of selected non-fatal cases for which a narrative has been submitted. The age listed in the narratives/listings refer to the age of the patient at the time to entry to the study, not to the actual age at the time of the event. Of note, a patient may have various identification numbers (SUBJID, USUBJID, IUSUBJID and a dummy ID) throughout different studies and documents. Throughout my review I use the USUBJID.

Tables throughout the body of this review refer to studies conducted with Daclizumab High Yield Process only (referred to as DAC or DAC HYP). Data from other daclizumab formulations (daclizumab Penzberg and Nutley) are not referred to as DAC in this review, are summarized in Appendix 13.3 and are not part of the Total DAC experience.

Anticipated areas of interest for the safety review

⁶ SDTM datasets are generated from study data collected during the clinical trial with minimal data derivations or imputation as opposed ADAM (analysis) datasets that are generated by the applicant, combining various datasets. Empirica Study only uses SDTM datasets.

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Daclizumab HYP is a monoclonal antibody (anti-CD25 IgG1 ab) that modulates T cell immunologic responses. As such, immunosuppression and immunogenicity are anticipated to occur with this biologic agent with the potential for increased risk of infections and malignancies with long term use, and development of anti-drug and neutralizing antibodies that could potentially increase the risk of immune reactions and/or decrease efficacy.

Based on the potential mechanism of action and prior clinical experience with DAC HYP, the following AEs were considered AE of interest in the applicant's Data Analysis Plan:

- Infections, including serious infections and potential opportunistic infections
- Cutaneous events
- Hepatic events
- Gastrointestinal events
- Anaphylaxis and hypersensitivity
- Autoimmune disorders
- Lymphadenopathy
- Hematological disorders and cytopenias
- Depression and suicide
- Malignancies
- Injection site reactions

Reviewer comment: Tregs are critical to maintaining immunological tolerance against self-antigens; T reg deficiency can lead to the development of autoimmune diseases. (1) Naturally occurring Tregs specifically express the transcription factor Forkhead box Protein 3 (FoxP3). Mice with mutation of FoxP3 develop "scurfy." The human equivalent of which is called Immune dysregulation Polyendocrinopathy X-linked (IPEX) syndrome. This syndrome is characterized by eczematoid or psoriasiform rash, autoimmune enteropathy and autoimmune endocrinopathy (e.g. thyroiditis, Type I diabetes mellitus) and other autoimmune diseases (e.g. autoimmune hepatitis, nephritis, cytopenias, alopecia). (1)(2)(3)

Several conditions cause "IPEX-like" syndromes, characterized by the IPEX phenotype without the genetic defect, including CD25 or IL2 receptor alpha (IL2RA) deficiency.(2)(42). This review will explore whether DAC HYP is associated with an IPEX-like phenotype. In addition to decreasing Tregs, DAC HYP induces a notable increase in NK cells of 50%. The applicant states that CD56(bright)NK cells appear to mediate some of the treatment related efficacy effects of DAC (the publication did not mention whether NK cell levels had any effect on safety)(4) .

Given DAC HYP pharmacodynamic effects (decrease in Tregs, expansion of NK cells) I am particularly interested on the evaluation of immune mediated events, and identifying cases consistent with an IPEX-like phenotype.

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8.2. Review of the Safety Database

8.2.1. Overall Exposure

At the time of the data cut-offs to support the filing, 2133 subjects with MS had received at least one dose of DAC HYP 150 or 300 mg every 4 weeks, including 1785 MS patients for up to 6 years accounting for approximately 4100 PYRs of exposure. Of these, 1215 were exposed for ≥ 2 years and 573 for ≥ 3 years. Of these 1215, 348 had previously been treated with IFN β -1a in Study 301 and received their first dose of DAC in study 303. At the time of the 4-month safety update report (SUR), submitted on 6/25/15 the total number of patients who received DAC HYP (either dose) was **2236 (5214 PYRS)**.

Table 4. Safety Population, Size and Denominators, BLA 761029 (SUR)

	DAC HYP (N=2353)	IFNβ1a (N=922)	Placebo (N=229)
Normal Volunteers* Total 145	127	0	25
Controlled trials for MS ¹	1336	922	204
All other trials for MS ²	170 133 597	0	0
Unique patients phase 2 & 3 trials, SUR	2236	922	204

* As per table 1 of SCS, DAC HYP studies in healthy volunteers. SUR= at time of Safety Update Report. ¹ Includes 417 patients from study 201 and 919 from study 301 (DAC HYP 150 or 300 mg q 4 weeks SC). ² Includes 170 patients who had received placebo in 201 and switched to DAC in 202; 133 patients from study 302 and 597 patients who received IFN in 301 and switched to DAC in study 303. (Source: Table in SUR, data not shown).

Table 5. Duration of Exposure

Number of patients with MS exposed to DAC HYP 150 mg or higher:			
Any exposure	≥ 12 months	≥ 24 months	≥ 36 months or longer
N= 2236	N= 1576	N= 1259	N= 888

*SOURCE: Original ISS and SUR (6/25/15). SUR data includes 395 exposed for 4 years and 211 exposed for 5 years. At the time of the original submission the total DAC experience (n=1785) included only 146 patients from study 303.

As per response submitted in October 6, 2014 at the time of the study 303 data cutoff for the original submission, only 146 patients had follow up data from study 303; 348 subjects had been dosed in study 303 but had no follow up data and were not included in the original ISS. For the 1785 unique subjects in the overall DAC safety population, the median number of doses of DAC HYP at any dose level was 28.0 (range: 1-74); 68% of subjects were exposed to 20 or more doses. Assuming no interruptions in treatment, subjects in the safety population had

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been treated with DAC HYP at the proposed marketing dose of above for a median duration of about 2 years, up to a maximum of almost 6 years. Of the 1785 unique subjects in the “Total DAC “ safety population there were 1492 subjects in the DAC150 analysis dose group and 293 subjects in the DAC300 analysis dose group.

At the time of the SUR the total number exposed to DAC150 was 1943, with no change in the number exposed to DAC300. The SUR includes 450 more subjects as compared to the original BLA, exposed for additional 1115 PYRs. (Source: Table in SUR, data not shown). As of the SUR, 211 patients had been exposed for up to 5 years. The median number of doses of DAC HYP at any dose level was 27 (25 doses for the DAC150 and 45 for the DAC300 group).

A summary of the number of patients exposed to DAC and the possible treatment sequences as of the SUR is shown below.

Table 6. Patients exposed to DAC HYP as of the Safety Update Report

DAC Treatment sequence	Number of patients
Study 201: DAC HYP 150	36
Study 201: DACHYP 150; Study 202: DAC HYP 150	17
Study 201: DACHYP 150; Study 202: DAC HYP 150; Study 203: DAC HYP 150	69
Study 201: DAC HYP 150; Study 202: Placebo / DAC HYP 150	17
Study 201: DACHYP 150; Study 202: Placebo / DAC HYP 150; Study 203: DAC HYP 150	69
Study 201: DAC HYP 300	34
Study 201: DACHYP 300; Study 202 DAC HYP 300	22
Study 201: DACHYP 300; Study 202: DAC HYP 300; Study 203: DAC HYP 150	65
Study 201: DAC HYP 300; Study 202: Placebo / DAC HYP 300	17
Study 201: DACHYP300; Study 202: Placebo / DAC HYP 300, Study 203: DACHYP 150	71
Study 201: Placebo; Study 202: DAC HYP 150	16
Study 201: Placebo; Study 202: DAC HYP 150; Study 203: DAC HYP 150	70
Study 201: Placebo; Study 202 DAC HYP 300	18
Study 201: Placebo; Study 202: DAC HYP 300; Study 203: DAC HYP 150	66
205MS301: DAC HYP 150	312
205MS301: DAC HYP 150; 205MS303: DACHYP 150	607
205MS301: 30 ug IFNβ1a; 205MS303: DACHYP 150	597
205MS302: DAC HYP 150	20
205MS302: DAC HYP 150/ Washout / DACHYP 150	113
TOTAL DAC HYP EXPERIENCE	2236

Source: MO JUMP analysis, Summary ADSL dataset, SUR. SUR cut-off: November 18, 2014. A total of 1943 subjects were exposed to DAC HYP 150 without any exposure to DAC HYP 300. 91 patients were exposed to DAC HYP 300 without exposure to DAC 150.

Reviewer Comment: Of the 293 patients in the DAC HYP 300 mg analysis group, 202 were exposed to DAC 150 for some part of the treatment. The number of patients exposed satisfies

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minimum ICH guidance recommendations for exposure for the DAC 150 mg dose. Safety tables for the Total DAC experience in this review will show pooled data for DAC 150 and 300 mg doses. Of note, this calculation of exposure is based on the assigned treatment, not on the actual treatment received by patients. The total number exposed includes 21 patients from site 903 in study 201, in which the pharmacist purposefully administered the wrong treatment (apparently provided active treatment to all patients).

Exposure in terms of patient years

Exposure in PYRs in the DAC HYP database was as follows (excerpted from the Summary of Clinical Safety):

In Study 201, mean (median) time on study treatment was similar across the treatment groups: 323.0 (337), 320.5 (337), and 321.9 (337) days in the placebo group, the DAC HYP 150 group, and the DAC HYP 300 group. The overall mean follow-up time in the study was 53.3 ± 10.12 weeks, with 635 subject-years accrued. Follow-up time was similar across the 3 treatment groups (placebo, 209 subject years; DAC HYP 150, 212 subject years; and DAC HYP 300, 214 subject years).

In Study 301, mean (median) time on treatment was 100.54 (111.43) weeks for the IFN β-1a group and 102.04 (108.71) weeks for the DAC HYP group. The total number of subject-years on treatment was 1776.56 years in the IFN β-1a and 1797.17 years in the DAC HYP group. Total number of subject years followed prior to alternative MS medication was 1882.05 in the IFN β-1a group and 1966.28 in the DAC HYP group. The total number of subject years followed up to 180 days following the last dose was 1872.88 in the IFN β-1a group and 1952.22 in the DAC HYP group. A total of 734 (80%) subjects in the IFN β-1a group and 771 (84%) subjects in the DAC HYP group remained in the study for at least 96 weeks.

The total DAC HYP exposure in PYRs at the time of the SUR was 5214 PYRs. As per information submitted on Jan 15, 2015 in response to FDA request, Exposure in terms of PYRs for male and female, separately at the time of the SUR was as follows: 3398.28 PYRs (1485 unique subjects) for females and 1815 PYRS (751 unique subjects) for males. As of December 21, 2015, overall exposure is 6634 PYRs; for females is 4311 PYRs and for males is 2323 PYRs and 1254 patients are still participating in DAC HYP trials.

The proposed labeling (under Section 6. ADVERSE REACTIONS. 6.1, Clinical Trial Experience) states:

It is unclear to me

(b) (4)

(b) (4)

8.2.2. Relevant characteristics of the safety population:

Demographic and clinical characteristics of the safety population for studies 201 and 301 are summarized below, from the applicant's tables.

Table 7. Demographic characteristics of study population in DAC HYP studies 201 & 301

		Placebo (N= 204) n (%)	DAC HYP 150 (N=208) n (%)	DAC HYP 300 (N=209) n (%)	IFNβ1a 30 (N= 922) n (%)	DAC HYP 150 (N=919) n (%)
Sex	Female	128 (63)	140 (68)	134 (64)	627 (68)	625 (68)
	Male	76 (37)	68 (33)	75 (36)	295 (32)	294 (32)
Age (years)	Mean (SD)	36.6 (0.02)	35.3 (8.94)	35.2 (8.67)	36.2 (9.32)	36.4 (9.36)
	Median	37	36	35	36.0	36.0
	Min, max	19, 55	18, 54	18, 55	18, 56	18, 56
Age Group ¹	18-19	1 (<1)	4 (2)	5 (2)	25 (3)	14 (2)
	20-55	203 (99)	204 (98)	204 (98)	896 (97)	(98)
Race	White	197 (97)	202 (97)	200 (96)	828 (90)	823 (90)
	Asian	7 (3)	6 (3)	9 (4)	28 (3)	27 (3)
	Other ²				66 (7)	69 (7)
Weight (kg)	Mean(SD)	69.99 (14.44)	68.31 (15.88)	68.20 (15.19)	70.92 (16.16)	72.16 (16.61)
	Median	68.0	64	66.50	68.0	70.0
	Min, Max	40, 141	38.2, 130	33, 118	42, 138	39, 136
Region ³	US & Canada	0	0	0	118 (13)	118 (13)
	Non US	204 (100)	208 (100)	209 (100)	604 (87)	601 (87)

¹ Two patients in study 301 (one in each treatment group) were 56 years old. No patients below 18 or >56 years were enrolled in either study. ² Data on race was collected; on ethnicity was not collected. Other: Black, American Indian or Alaska native, other and not reported. ³ Region 1= US & Canada; Non US= Region 2 (Western Europe, Australia & Israel) & Region 3 (Eastern Europe, Mexico, Argentina, India & Brazil). Source: Extracted from Tables 15, study 201 CSR and Table 18, study 301 CSR.

Treatment groups were well balanced in regards of age, gender, race, weight and region and similar to those in clinical trials with other products conducted for the MS indication. Mean age at entry to DAC HYP controlled trials was 36 years. There were very few patients in the 18-19 years group (n=49) or ≥56 (n=2) among the two studies at entry. Study 201 included only non-US patients. Study 301 included patients from US and Canada (13% of patients in study 301). The highest recruitment was from Region 3 (Eastern Europe, Mexico, Argentina, India and Brazil) (65% of patients in study 301).

Regarding the characteristics of the Total DAC HYP database (n=2236), there were 1485 female and 751 male, with a mean and median age of 36 years (range 18-56 years) at entry. The country with the most patients was Poland (25%) followed by Russian Federation (14%), Czech Republic and Ukraine (9% each) and the United States (8.5%). Other individual countries recruited less than 5% of patients each (0.05% to 5%).

Reviewer Comment: The age entry criterion was 18 to 55 years. Limited data exist for patients >55 (from patients who participated in DAC HYP trials for several years). There is no data in

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patients older than 65 years in this application. Patients were mostly White (90-97%), with small representation of other races/ethnicities, which is a limitation FDA encounters in most applications. Data on race was not collected in some countries because of local regulations. Data on ethnicity was not collected at all. Given the small number of patients who were older than 55 years and of patients of race other than White, it is not possible to draw any conclusion regarding the influence of age or race on the safety profile of DAC HYP. It is desirable that further clinical trials in MS clinical programs allow inclusion of patients older than 55 years and diverse races/ethnicities.

Other Baseline Characteristics (e.g., disease characteristics, important concomitant drugs)

MS disease characteristics and prior treatments for MS were balanced among treatment groups, in both controlled studies. At entry patients had moderate disability, with a mean EDSS of 2.6 (possible range is 0 to 10, 10 meaning death because of MS). Mean duration of symptoms before entry was approximately 7 years. In study 201, most of the population had at least one relapse within year prior to entry; in 301, 43% had ≥ 3 relapses within the 3 years prior to entry. (Source: Tables 16 and 20, study 201 and 301 CSRs, respectively. Data not shown.)

Overall, in study 201, only 16% of patients had been treated with previous drugs specifically approved for MS (mostly IFN β , followed by glatiramer). This was a smaller percentage as compared to approximately 40% of patients previously treated with an MS drug in study 301. In study 301 previous treatment was also mostly IFN beta (including 22% treated with an IFN β 1a, the active comparator drug in this trial), followed by glatiramer, mitoxantrone and natalizumab. Overall in study 301, 11% were treated with MS drugs other than IFN β or glatiramer, including corticosteroids. (Sources: Tables 18 and 24 of studies 201 and 301 CSRs, respectively. Data not shown).

Regarding comorbid conditions, medical history was similar across groups in each study. The most common medical history was genitourinary, musculoskeletal and gastrointestinal for both, 201 and 301 (ranged roughly from 20-27% of patients for these AE categories). A previous history of dermatologic, allergic and hepatic conditions was reported in 10%, 9% and 4% of patients, respectively in study 201, and 16%, 15% and 4% of patients, respectively in study 301. (Data not shown.)

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Patient disposition

Patient disposition in the controlled trials, as presented by the applicant is shown in the following table.

Table 8. Patient disposition in Studies 201 and 301

	Study 201			Study 301	
	Placebo	DAC 150	DAC 300	IFNβ1a 30	DAC 150
Randomized (and dosed)	204	208	209	922	919
Completed treatment	186 (91)	189(91)	192 (92)	644 (70)	653 (71)
Withdrew drug treatment	18 (9)	19 (9)	17 (8)	278 (30)	266 (29)
WD drug because of AE	2 (<1)	6 (3)	9(4)	83 (9)	130 (14)
other than MS relapse					
Withdrew from the study	18 (9)	20 (10)	15 (7)	228 (25)	195 (21)

Source: Tables 14 and 28, study 201 CSR, and Table 17 of study 301 CSR.

A higher percentage of patients completed the one-year study (91 %) as compared to the 3 year study (70%) but similar percentages completed treatment in each arm in each study. Patients who completed the study treatment could be enrolled into an extension study (202 and 303 for 201 and 301, respectively). Patients who discontinue drug treatment were to continue in the study for the 180 follow up period. The most common reason of drug discontinuation in 201 was consent withdrawn (4% overall), followed by AE (3% overall). The most common reason of drug discontinuation in 301 was AE (11% overall) followed by consent withdrawal (9% overall).

Reviewer Comment: There are slight discrepancies between the applicant's disposition tables as presented in Table 8 of this review and the analyses generated with Empirica Study. Some of these discrepancies may be because the reasons for withdrawal entered in the CRFs were re-classified by the applicant prior to unblinding. For further analyses of Disposition and protocol deviations see Dr. Rodichok's review. My analyses of studies 201 and 301 use 207 and 208 patients as denominators for the DAC HYP 150 and 300 doses respectively.⁷ My analyses of the Total DAC HYP Experience (done with JUMP from the ADAE3 dataset) use 2236 patients as denominator.

⁷ As per the applicant's disposition table a total of 208 and 209 patients were dosed with DAC HYP 150 and 300, respectively in study 201. As per analyses generated by Empirica Study (which uses SDTM datasets), two patients do not have record of participation in the study (201/109-004 and 201/765-001 in the DAC 150 and 300, respectively). Both withdrew consent and had the End of Study Visit on Day 1. Patient 201/109-004 was randomized to DAC HYP 150 and received 1 dose of DAC HYP 50 mg on April 20, 2010. Patient 201/765-001 was randomized DAC HYP 300 and as per Empirica Study did not receive any dose. However, as per the Disposition ADAM dataset, this patient did receive 1 dose before withdrawing consent. This is a minor difference (one less patient in each active treatment group). The analyses of AE rates generated with Empirica Study were very consistent with those generated by the applicant.

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Patient compliance, Concomitant Medications, and Rescue Medication Use during the study

Compliance⁸

The percentage of subjects who received all planned doses in the placebo-controlled study was similar across treatment groups, although slightly higher in the placebo group (87% placebo group, 84% for DAC HYP 150 mg group, and 81% for DAC HYP 300 mg group) [study 201 CSR, Table 19]. In study 301, a total of 734 subjects (80%) in the IFN β -1a group and 771 subjects (84%) in the DAC HYP group remained in the study for at least 96 weeks (study 301 CSR, Table 74). Overall compliance in the Total DAC experience was not analyzed.

Rescue and concomitant medications⁹

IV Methylprednisolone (MP) was allowed for treatment of MS relapse at the discretion of the treating neurologist in all protocols. Concomitant use of IFN- β was permitted in the study protocols in studies 201 (after the first 6 months) and in 202, and 203, provided the subject had experienced a relapse. In Study 302, subjects were allowed to use IFN- β during the 20 week washout period but were required to discontinue use prior to re-initiating DAC HYP in the extension phase of the study.

In study 201 approximately one-quarter of randomized subjects (26%) used corticosteroids (CS) at some point during the study. The most common concomitant medication was IV MP in 36%, 18% and 20% of Placebo, DAC 150 and DAC 300 groups, respectively. Other CS were used by small numbers of subjects (<4% total). The use of other commonly used concomitant medications was balanced among treatment groups including paracetamol (17% overall), omeprazole (11% overall), ibuprofen (10% overall), and potassium (7% overall).

In study 301 the most frequently used concomitant medications included paracetamol (76% in each group); ibuprofen (higher use in the IFN β -1a group (41%) as compared to DAC HYP 150 (33%); methylprednisolone (MP) also higher in the IFN β -1a group (43%) as compared to DAC HYP 150 (32%); omeprazole (20% and 15% on IFN and DAC HYP 150 respectively); and amoxicillin (with slightly higher use in the DAC HYP group [14%] as compared to IFN β -1a [11%]). Paracetamol, ibuprofen, naproxen, and aspirin were protocol-specified medications that subjects were instructed to take for the first 24 weeks of the study to reduce flu-like

⁸ As per applicant's Integrated Summary of Clinical Safety.

⁹ Summarized from tables in Integrated Summary of Clinical Safety. This is a complex database and I was not able to replicate the applicant's numbers. The terms for concomitant medications are not standardized in the datasets. Even after standardizing terms (with help of Dr. Ana Szarfman using Empirica Study), I could not exactly match the numbers presented by the applicant. Of note, the datasets for concomitant medications included some medical and surgical procedures.

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symptoms; additional dosing was allowed if needed. IV MP was the protocol allowed treatment for MS relapse. *The imbalance observed in the use of concomitant meds is consistent with a higher incidence of flu-like symptoms and MS relapses in the IFNβ1a group.*

Use of concomitant meds in Total DAC HYP experience

As of the SUR, the most common concomitant medication was paracetamol (48%); methylprednisolone (31%), ibuprofen (26%), omeprazole (16%), amoxicillin (11%), and amoxiclavulanic (10%) were the most frequently used medications by ≥10% of subjects.

Reviewer Comment: The applicant provided analyses of concomitant medications but for some drugs such as corticosteroids, it is unclear whether they were topical or systemic, or whether they were administered during or after DAC HYP was stopped. Dr. Rodichok has requested additional information regarding corticosteroid use. A response is pending at the time of this review.

Use of Alternative MS medications⁸

A small number of patients used alternative MS medications during study 201. IFN-β was taken as a protocol-allowed concomitant medication after the 6th month of treatment in 7 subjects in the study (5 in the placebo group and 1 each in the DAC 150 and DAC 300 groups). One subject on DAC HYP 300 used azathioprine and one used glatiramer (on placebo). (Source: Table 50, CSR study 201, data not shown).

In study 301, 6% of subjects in the IFNβ-1a group and 5% in the DAC HYP group started alternative MS medication. The most commonly used alternative MS medications were IFNβ1a (2% in each treatment group); natalizumab (2% in the IFNβ-1a and <1% in the DAC HYP 150 group), and glatiramer acetate (<1% in each group). Therefore except for natalizumab the use of alternative meds was similarly distributed. (Source: Table 78, CSR for study 301)

A total of 132 patients (6%), received alternative MS medication in the Total DAC experience including IFNβ1a. The use of alternative MS meds in the Total DAC HYP pool as of the SUR is presented below.

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Table 9. Table of Alternative MS medications in Total DAC HYP experience, SUR

	TOTAL DAC HYP N=2236 n (%)
Subjects taking alternative MS meds	132 (5.9)
INTERFERON BETA-1A	68 (3.0)
TACROLIMUS	12 (0.5)
GLATIRAMER	11 (0.5)
NATALIZUMAB	10 (0.5)
INTERFERON BETA-1B	7 (0.3)
AZATHIOPRINE	6 (0.3)
CYCLOPHOSPHAMIDE	5 (0.2)
FINGOLIMOD	5 (0.2)
FUMARIC ACID	5 (0.2)
TERIFLUNOMIDE	5 (0.2)
METHOTREXATE	3 (0.1)
IMMUNOGLOBULIN G HUMAN	2 (0.1)
IMMUNOGLOBULIN	1 (<0.1)
IMMUNOGLOBULIN HUMAN NORMAL	1 (<0.1)
MITOXANTRONE	1 (<0.1)
RITUXIMAB	1 (<0.1)

Source: Table 32 of SUR. Includes DAC HYP 150 and 300 mg. Medications considered concomitant if taken on or after date of first dose of DAC HYP up to 180 days after last dose of DAC HYP (it does not include interferon beta-1a as part of assigned treatment in study 301).

A small number of patients used alternative MS therapy during or after stopping DAC HYP (total of 5.9%). As per Table 31 of the SUR, 75 patients used IFN β (1a or 1b) in the Total DAC (3%). Of those, 31 (1%) initiated IFN after the last dose of DAC; 30 (1%) suspended DAC while taking IFN and 14 (<1%), received DAC while taking IFN (data not shown). The most common non-IFN β1 alternative meds were tacrolimus, glatiramer and natalizumab (each used by 0.5% of patients).

The table above includes 12 patients on tacrolimus. As per information submitted on 3/3/16, tacrolimus was topical for cutaneous condition.

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8.2.3. Adequacy of the safety database

The overall exposure to DAC HYP fulfills minimum ICH Guidance criteria for premarketing evaluation of a drug/biologic agent intended for chronic use for DAC HYP 150. However, this is an agent with many potential long-term biologic effects (e.g. increased risk of opportunistic infections, malignancies). The demographics and disease characteristics in this database are consistent with that of other applications for MS. The limited information on races other than White does not allow conclusions on safety of DAC HYP by race or ethnicity.

8.3. Adequacy of Applicant's Clinical Safety Assessments

8.3.1. Issues Regarding Data Integrity and Submission Quality

Safety monitoring of patients participating in the trial was appropriate in general. Subsequent to the death from liver failure in study 202 (patient 909-001), all protocols were amended to emphasize eligibility, monitoring and discontinuation criteria with regards to serious hepatic and cutaneous toxicities, all measures that further enhanced patient safety. The original controlled trials already had liver enzyme measurements every 4 weeks but the rule for interruption was ALT >5xULN instead of >3xULN.¹⁰

Protocol violations/deviations are being evaluated by Dr. Rodichok. With the purpose of evaluation of safety, a major protocol deviation occurred in study 201, site 903, in which the pharmacist purposely dosed all 21 patients with DAC HYP instead of the assigned treatment. Patients in site 903 were not excluded from safety analyses. The type of adverse events these patients presented could be consistent with either active drug or placebo (except for a case of diabetes insipidus that it is likely to have occurred with active drug). The intent to treat analysis appears acceptable.

Collection and presentation of data for safety analyses in this application is poor. Information is hard to find and the quality of the datasets and narratives submitted in this application are far from desirable.

A data fitness session conducted by OSC JumpStart team at the time of filing identified several deficiencies in the AE datasets such as the presence of empty cells in the Outcome variable

¹⁰ An independent Data Safety Monitoring Board (DSMB) met regularly to review data from the MS studies. An external independent panel of hepatology experts (referred as to the Hepatic Adjudication Committee (HAC)) evaluated selected hepatic events. For cutaneous reactions a single, blinded, independent dermatologist (referred to as the Central Dermatologist) periodically reviewed clinically significant events. However, these experts evaluated cases retrospectively; they did not make recommendations on management of individual patients at the time of the events.

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(AEOU), the lack of SAE categorization (fatal, life-threatening, hospitalization, etc.), the lack of CDISC terminology for the LAB, ECG and Vital signs domains, and the lack of an EPOCH variable (which is useful to have when a single patient participates in sequential studies). In order to expedite our reviews, on April 30, 2014 DNP requested updated datasets for a limited number of domains and variables to correct some of the deficits mentioned above, for individual studies and for the Integrated Summary of Safety. The applicant submitted updated datasets on May 14, 2015. Of note, for the AE Outcome variable, in response to the FDA comment that cells should not be empty, the applicant filled out all previously empty cells with the word “unknown.” Moreover, an end date for an AE in the AE datasets did not necessarily mean that the event came to an end. As part of the Define files for the SUR, the applicant clarified that the value “unknown” was assigned to AEOU even in the cases where the event end date was present for the following reason (verbatim from applicant): “If an event changes seriousness or severity, for the purposes of the case report form, the original event is marked as ended and a separate event is started. For events with an end date, it is uncertain whether the event resolved, or rather if the characteristics of the event changed to require a separate AE record. Therefore, it was decided that if the event was not fatal (per criteria above) or explicitly marked as Not Resolved, then the outcome variable AEOU would be assigned to UNKNOWN.”

As of the SUR (cut-off of November 2014, submitted June 25, 2015), approximately 60% of patients with AE had at least one AE with no end date in the ISS AE dataset, including 127 out of 710 (18%) patients with SAE or AE leading to withdrawal (WD). As per a response to a DNP request for follow up of these patients submitted on September 28, 2015, roughly 7% of patients with SAE or AE leading to WD in the ISS, still had at least one event that was unresolved (event could be ongoing or could have no follow up). (Information was not requested for non-SAE or events that did not lead to withdrawal). For more detail see Section 13 (13.3.17) of this review.

As per review of individual follow up IND safety reports, some events reported as “resolved” in the September 28, 2015 response, should not have been categorized as such, because the patients were still taking corticosteroid or immunosuppressors to treat the AE (e.g. ID# 203/506-011, case of autoimmune hepatitis).

Moreover, review of the narratives and patient profiles indicates that many events listed as “no action taken with drug” in the AE datasets included cases in which in fact, the drug was no longer administered (e.g. it was stopped for other AE that occurred on the same day or an AE prior to this event, or because it was the last dose at the end of a study for which there was an extension [and the patient did not enter the extension]). As per the FDA analysis of cases listed as interrupted because of AE in the Hepatobiliary SOC, 14% never re-started drug. Analyses of response to de-challenge based on “no action taken with drug” do not accurately reflect the number of patients who stopped drug.

Of note, the AE datasets included the study relative onset day for an event, but did not include

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the number of doses of DAC received before the event. This information is in the narratives, but cannot be analyzed from the datasets. Identification of the total number of doses received before an event is particularly cumbersome for the extension studies. Additionally, the concomitant medications datasets do not use standard terminology and are unclear as to whether medications were used during or after DAC HYP was stopped. For instance, analyses of “alternative MS medications” in the DAC HYP database include 12 patients on tacrolimus, which is unlikely to have been used to treat MS.

Also, in general, the narratives were long and repetitive, and some presented conflicting information for the same event (see example of applicant’s narrative, [section 13.3 (13.3.2) of this review]). A narrative might state that the patient continued into the extension but the patient is not found in the extension study (e.g. 201/454-007 with Crohn’s disease). Moreover, by reading the narratives I identified several events that were not captured in the datasets, such as the case of an attempted suicide by benzodiazepine overdose (patient 301/128-003), a case of severe anemia with HTC of 21% requiring transfusion in a patient with pneumonia (302/162-107), and a case of interstitial lung nodules in a patient with skin rash and lymphadenopathy suspected of Drug Reaction with Eosinophilia and Systemic Symptoms (303/609-013) or a case of pancytopenia requiring bone marrow biopsy in a patient suspected of brucellosis (303/453-048).

Importantly, many patients underwent invasive medical and surgical procedures for workup of conditions potentially associated to drug use (e.g. colonoscopy, duodenoscopy, mediastinoscopy, lymph node, skin, lung, kidney and liver biopsies). These events were not included in the AE datasets. Some of these procedures captured in the concomitant medications dataset (under the concomitant non-drug treatment category), but most cases can only be identified by individual review of the narratives. For instance, there is only one liver biopsy listed among the concomitant non-drug treatments, but there were at least 8 liver biopsies in this clinical program.

An additional factor that complicated the review and interpretation of the data is that a same patient could have different identification numbers in different documents. While the integrated summary of safety and the safety update report used the dummy ID, the individual study reports and the consultants’ reports (e.g. Hepatic adjudication committee) use the subject identification (SUBJID) or the unique subject ID (USUBJID).

In summary, in addition to the fact the application is extremely difficult to navigate, the datasets are not reliable in terms of whether drug was discontinued or not or with respect to reversibility and outcome of AEs. Moreover, relevant events may have not been captured, such as invasive diagnostic procedures.

8.3.2. Categorization of Adverse Events

The dictionary used to code AE was the Medical Dictionary for Regulatory Activities (MedDRA).

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Study 201 used MedDRA 14.0 and study 301 and extension studies used MedDRA 16.1. The ISS datasets used MedDRA v. 16.1. All analyses of AEs were based on the principle of treatment emergence or worsening of an event that was present prior to starting treatment. Because of the long half-life of DAC HYP, analyses of AEs included events with an onset date up to 180 days after study drug discontinuation, regardless of whether or not alternative therapy was received. This approach is appropriate.

Regarding coding, various-PTs were used for the same event (“splitting”). For instance drug induced hepatotoxicity was reported using the following PTs: Drug induced hepatitis, Drug induced liver injury, Hepatitis, Hepatitis toxic, Jaundice, Jaundice hepatocellular (under the Hepatobiliary SOC) or elevated liver enzymes (under the Investigations SOC). Additionally, some potential cases of DILI were included in the Infections and Infestations SOC (e.g. “hepatic yersiniosis” [201/752-018] without support for the diagnosis of Yersinia infection).

Similarly, terminology for cutaneous events varied among different investigators (e.g. dermatitis, allergic dermatitis, atopic dermatitis, eczematous dermatitis, eczema). It is unlikely that a non-dermatologist investigator can distinguish among various forms of dermatitis, psoriasis, vasculitic, infectious and other possible rashes. The Central Dermatologist reviewed approximately 500 clinically relevant cutaneous events. As per his report, he tried to use a consistent nomenclature and assess causality for these events. However, in response to an FDA request for the dermatologist’s nomenclature, the applicant stated that this information had not been collected.

Splitting was also observed for AE consistent with inflammatory bowel disease (colitis, ulcerative colitis, microscopic colitis, enterocolitis, etc.) and for events consistent with immune mediated lung disease (alveolitis, interstitial lung disease, idiopathic pulmonary fibrosis, etc.).

Additionally, with regards to categorization of SAE, based on the narratives, some events categorized as “non-serious” were in fact important medical events that should have been categorized as serious, for instance a case of “non-serious” rash involving the soles of the feet to the point “she was barely able to walk” (301/512-002) or a case of “non-serious” vasculitis and exfoliative dermatitis that led to drug withdrawal (301/606-019). These events should be considered serious, in the case of 301/512-002 because of significant disability (this AE was later categorized as serious when the patient was hospitalized with worsening rash); and in the case of 301/606-019 because it could become life-threatening if not adequately treated. As mentioned earlier, the datasets do not include variables for categorization of SAE.

Moreover, a serious AE that required hospitalization would be reported as having an end date the day of hospital discharge, to be “downgraded” to a non-serious event, even if the adverse event did not resolve. Also, sometimes a patient would have several ongoing AEs but only one would be determined to be serious, for instance, a case of a patient who was hospitalized with

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aspiration pneumonia and sepsis, in which the case of sepsis was “serious” but the pneumonia, was “non-serious” (303/611-015).

In summary, there is extensive splitting of terms and miscategorization of serious AEs in this application.

8.3.3. Routine Clinical Tests

The routine clinical and laboratory evaluations were adequate in general but are notable for the lack of measurement of glucose and calcium in the controlled studies. Uric acid and phosphorus were not collected either. In response to a DNP request for clarification, the applicant stated that since there was no evidence of glucose or calcium disturbances in the daclizumab Penzberg, studies, it was decided not to include these measurements in studies 201 and 301 of DAC HYP. Of note, study 302 did include calcium and glucose measurements (but the study is small (113 patients), short (6 months) and uncontrolled).

Information on glucose levels may be relevant to the diagnosis of Type I diabetes mellitus, one of the potential manifestations of autoimmunity. Of note, the Zenapax label (daclizumab Nutley) carried a precautionary statement regarding hyperglycemia and increased fasting glucose levels, which is something the applicant should have evaluated with DAC HYP. If as the applicant proposes, DAC HYP is biologically different from other daclizumab formulations, omitting routine glucose and calcium levels does not appear to be justified either. Moreover, 22 patients had adverse events with preferred terms consistent with diabetes in the ISS (hyperglycemia, diabetes mellitus, diabetes mellitus type I, diabetes ketoacidosis, impaired glucose tolerance), however, there are no glucose measurements in these patients. The lack of available calcium levels hampers the evaluation of patients with fractures, lithiasis and of potential cases of sarcoidosis (which given the number of patients with lymphadenopathy in this application, would have been very helpful to have).

In summary, the quality of the submission in terms of data collection, follow up of patient outcomes, categorization of AE, coding and presentation for safety analyses is poor. Because of the uncertainty of the outcome in a substantial number of patients, of the accuracy of some end of AE dates, whether the drug actually was continued or not, whether events actually resolved, and whether all relevant events were actually captured in the datasets, analyses of incidence, duration, reversibility and response to drug discontinuation because of adverse events generated from these datasets are likely to be inaccurate and under-represent the extent of toxicity associated with this product.

*Despite its limitations, in my opinion the information submitted in this application has raised safety concerns that warrant a **Complete Response**.*

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8.3.4. Evaluation of dose response

Dose selection for the phase 2 trial 201 was based on estimations from study DAC-1012, a placebo controlled study of two dose regimens of daclizumab Penzberg (high-dose [2 mg/kg SC every 2 weeks] and low-dose [1 mg/kg SC every 4 weeks]) in 230 patients with MS receiving concurrent IFN- β therapy. Results from this study are discussed in Section 13 of this review. PK and PD analyses were done in a subset of patients (<70 patients) (to be reviewed by Clinical Pharmacology team).

The phase 2 study in MS (Study 201, described earlier in Section 5) is the only study that allows direct comparison of DAC150 and DAC300. As per my evaluation, there is a suggestion of a dose response for some AE between 150 and 300 mg (e.g. skin reactions), but no dose response in terms of most AE, labs and vital signs in this study. The size and duration of this study (approximately 200 patients per group, placebo-controlled for 1 year) does not allow extensive assessment of dose response in terms of safety, particularly for immune related events that may be idiosyncratic.

The applicant presented the total DAC HYP data in three columns: DAC150, DAC300 and Total DAC experience. As of the SUR, the DAC150 group included 1943 patients; the DAC300 group included 293 subjects who had received at least one dose of DAC300 (but 202 of those subjects also received one or more doses of DAC150, see Table 6 of this review). The DAC 150 and 300 mg groups are not randomized. The grouping is somewhat arbitrary. Moreover, patients in the DAC150 group received a median of 25 doses, while patients in the DAC300 group received a median of 45 doses. Regardless of the approach used to analyze the data, it is not possible to draw definitive conclusions regarding the safety of the 300 mg dose as compared to the 150 mg dose in the Total DAC HYP database.

The Total DAC HYP database is inadequate for evaluation of dose-response. When discussing the Total DAC HYP database this review will only show the pooled data from the two dose groups (N=2236 patients).

8.4. Safety Results

8.4.1. Deaths

As of October 31, 2014 there were 10 deaths in the DAC HYP development program. Five in patients who had received DAC HYP (four in the DAC150 and one in the DAC300 group) and five among patients who received IFN β 1a. No additional deaths were reported in this application. Autopsies were available for two of five patients who died while or after receiving DAC HYP. No autopsies were available for the other patients. Documentation of due diligence for all cases was included in the submission. Deaths are summarized below.

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Table 10. Deaths in the DAC HYP development program

Unique Subject ID/ (Dummy ID)	Age, sex, country	Last dose/ Death (Study day)	Cause of death
DAC HYP 150 mg			
201/304-006	49 F/UK	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. (See narrative after table)
301/431-004	37 F/France	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 (See text after table)
301/744-007	46 F/India	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. (See narrative)
303/537-012	39 F/Russia	171/193 (550 since start)	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.
DAC HYP 300 mg			
202/909-001	45 F/Ukraine	225/325 (of study 202) (702 since start)	Autoimmune hepatitis, liver failure, multiorgan failure. Patient received DAC 300 in study 201, 5 doses of placebo in 202 (6 months off-DAC HYP); re-started DAC 300 (4 doses) with rapid ALT increase and decline in liver function leading to death. (See narrative for additional information)
IFN- β1a.			
301/536-005	40 M/Russia	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/Russia	142/ 148	Peritonitis after laparotomy for abdominal pain, after 20 weekly doses of IFN. No additional information is available.
301/641-026	41 M/Ukraine	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/Czech Rep	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/India	55/284	Progression of MS approximately 7 months after stopping IFN.

Source: Table 7, listing of deaths, applicant’s SCS and review of individual CRF and patient profiles. See additional discussion below.

Narratives of the five fatal cases on daclizumab HYP are as follows.

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201/304-006, 49 year-old female with medical history of rash with penicillin and trimethoprim. Started DAC HYP 150 mg on (b) (6). Her last treatment dose was on (b) (6) (at Week 44, 12th dose of DAC, **Day 308 of study**). This patient presented elevated ALT since Day 169 in study 201. Drug was discontinued on Day 308 because of elevated ALT and AST (up to 3x ULN) and mild increase in ALP. Concomitant medications included ibuprofen and amitriptyline (long term use before entering the trial); topiramate was used shortly from Day 140 to 184; propranolol had been started on Day 195, and pregabalin on Day 251. Liver enzymes improved after DAC HYP discontinuation. She had developed a mild forehead rash upon the first dose of DAC HYP that had resolved without specific treatment.

On Day 326 (2 ½ weeks after last dose of DAC) she developed a severe cutaneous drug reaction that led to hospitalization on Day 380 and was complicated with bacteremia (positive blood cultures for staph aureus), bilateral retinal vein thrombosis, psoas abscess and ischemic colitis. The rash was described as extensive maculopapular rash on feet, hands chest, abdomen and back; desquamative; with mucosal involvement. A skin biopsy was consistent with a drug reaction “of the lichenoid type.” Anti-DAC antibodies and neutralizing antibodies were present since Day 169.

The patient developed progressive **erythroderma with desquamative lesions** and was treated with oral steroids and creams. She then was admitted to the hospital with worsening rash, developed bilateral retinal vein occlusion and started anticoagulation complicated with GI bleeding requiring resuscitation. She died on (b) (6). The anticoagulant therapy, septicemia and abnormal liver function cumulatively led to bleeding into the psoas abscess and hematoma which probably resulted in thrombosis of the vessels supplying the descending colon. Regarding the liver, the autopsy states that “Liver was autolyzed so the pathology was difficult to interpret.”

Reviewer Comment: In my opinion this death is related to study drug. Based on the autopsy the ultimate cause of death was psoas abscess (infection and bleeding) causing ischemic colitis but the process seems to be an infectious complication of a severe cutaneous reaction after drug discontinuation because of increased liver enzymes. ALT and ALK were elevated since Day 169, and reached 3x ULN on Day 308 (which was the date of last dose). WBC was stable throughout the study. There was no evidence of eosinophilia. The description of the rash does not allow classification other than to say that it is consistent with a drug induced serious cutaneous reaction (it does not allow to determine whether this was SJS/TEN or Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) (because of liver involvement). Of note, anti-DAC antibodies and neutralizing antibodies were present since Day 169. The role of these antibodies is unclear.

202/909-001 – Fulminant autoimmune hepatitis. 45 year-old female from Ukraine with history of photoallergy and chronic pyelonephritis. No history of drug allergy. She received one year (13 doses) of DAC HYP 300 as part of study 201. Mild ALT elevation was observed at screening

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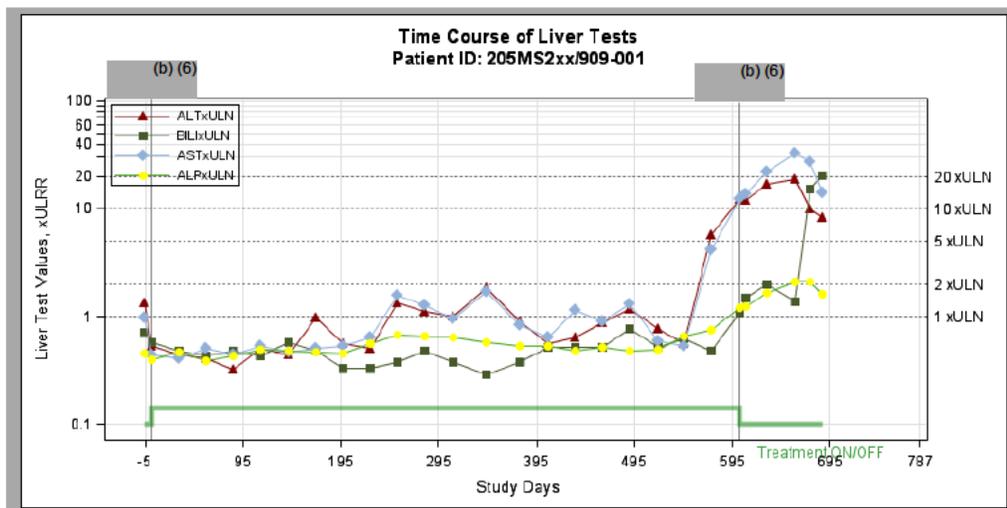
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(1.3 xULN), but was normal on weeks 0 through 32 in study 201. Then again there was mild elevation on weeks 36 to 48 (<2x ULN). A “cutaneous event” was reported on Week 44 during study 201. She was then randomized to receive 5 months of placebo washout, to be followed by 8 doses of DAC 300 mg in study 202. She received 5 doses of placebo (every 4 weeks, from (b) (6) [Week 0, Day 1] through (b) (6) [Week 20, Day 142 of study 202]). On (b) (6) (Day 137, still on placebo) she presented MS relapse treated with IV MP x3 and tizanidine (until Day 152). ALT & AST were normal during placebo treatment. A slight elevation (<1.3 xULN) was observed at week 16 of placebo but was normal at week 20.

She then received 2 doses of DAC HYP 300 (Day 141 and Day 167) in study 202. ALT & AST were normal at week 24 (Day 167). Non-SAE of mild ALT and AST increase were reported on Day 192. On (b) (6) (Week 28, Day 197, on the day of the third DAC dose ALT was 5.7x ULN and AST was 4x ULN with normal BR. The last dose (fourth dose) was on (b) (6) (Week 32, Day 225). On that date ALT and AST were 12x ULN. BR and ALK phosphatase were slightly elevated. Subsequently, DACHYP 300 treatment was withdrawn because of severe increase in ALT & AST and Hepatitis of unknown etiology. Maximum ALT was 18 x ULN and AST was 33 x ULN on Day 282 but persisted elevated in the 8x ULN range thereafter. Maximum available total BR level was 20x ULN on Day 310. Graphic presentation of the course of liver enzymes is shown below (using FDA eDISH).



On (b) (6) (Day 291 of study 202) she was diagnosed with Autoimmune hepatitis and jaundice. Hepatitis and HVS serology was negative. ASMA, AMA, SLA and LKM-1 and ANCA antibodies were negative. She developed encephalopathy, ascites, and edema of the legs and the feet. WBC count had been around $6 - 9 \times 10^9 / L$ throughout studies 201 and 202, with normal differential, and no increase in eosinophil count. On Week 30, labs showed 1% atypical lymphocytes. After the diagnosis of hepatitis was made she was treated with Hepabene, cyanocobalamin, pyridoxine, arginine, and ursodeoxycholic acid (Urso), and later with activated charcoal, furosemide, prednisolone, bile therapy, lactulose, IV MP x3.

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On (b) (6) she died (Day 325 of study 202, Day 702 since initiation of therapy in study 201, approximately 3 months after the last dose of DAC). As per the autopsy, the cause of death was fulminate **hepatitis with liver and multiorgan failure** and disseminated intravascular coagulation, with liver histology consistent with **autoimmune hepatitis**. The liver showed postnecrotic liver cirrhosis with 2-10 mm nodules of friable consistency. Histology showed marked leukocytic lymphohistiocytic and plasma cell infiltrate of periportal tracts and interlobular partitions with multilobular cirrhosis, fibrous tissue, regenerative nodes from enlarged and multinuclear hepatocytes, intracellular deposits of yellowish brown pigment, ballooning, fatty degeneration of hepatocytes, necrosis of liver lobules and hemorrhages. Anti DAC and neutralizing antibodies were negative at all times.

Reviewer Comment: At the time of the event, the investigator did not suspect that this was related to study drug. A relationship to DAC is supported by Drs. John Senior and Mark Avigan, two FDA hepatologist who reviewed this case, as well as by the members of the Hepatic Adjudication Committee. After this patient's death, the protocols were amended to ensure that drug was interrupted if ALT values were >3xULN and that the investigator had to see the labs before the next dose. Had the patient not received the fourth dose of DAC HYP, the outcome may have been different. For further discussion of daclizumab-induced liver toxicity see section 8.5.1 (Analysis of Submission-Specific Safety Issues: Drug-Induced Liver Injury).

301/431-004 – Aspiration pneumonia/septic shock. 37 year-old female from France with MS, with history anaphylaxis (unclear trigger). She had received MS treatment with glatiramer and IFNβ1a several years prior to entry. She had had 2 relapses within the last 3 years prior to entry. Her most recent MS relapse was in November 2011. EDSS at baseline was 3.5. She began treatment with DAC HYP 150 mg (b) (6) and received 3 doses. Last dose was on Day 58. On Day 85 (3 weeks after the last dose) patient presented **palmo-plantar dyshidrotic eczema and sialadenitis of the mouth**. The events were categorized as “non-serious” but led to drug and study withdrawal. The eczema was treated with topical steroids. One month after the onset, a follow up dermatologic assessment found favorable progress in the hands with a desquamated, slightly fissural appearance but “very unfavorable outcome in the feet.” The events of palmo-plantar eczema and sialadenitis **did not resolve**. DAC antibodies were negative on weeks 0 and 4 but positive at week 12 (on Day 87 value was 120, no units provided). Neutralizing antibodies were negative. A repeat DAC antibody on Day 91 was negative. On Day 132 (approximately 2 months after last dose of DAC HYP) she presented a **severe MS relapse** with tetraparesis, dyspnea, difficulty swallowing, facial paralysis and acute respiratory distress syndrome. EDSS score was 9. The narrative states that an MRI showed several subtentorial lesions as well as lesions in the medulla and that “the brainstem was likely involved in the MS relapse.” However, details of MS relapse and MRI are not included in the CRF, narrative or patient profile. EDSS assessment at screening had not shown signs of brainstem involvement. On Day 136, small intestine occlusion was reported. There is no other information about this event.

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On Day 139 she developed respiratory distress and was transferred to the Surgical ICU. Labs showed hematocrit of 34.1% (as compared to 45% at screening), WBC of $10.4 \times 10^9/L$ (as compared to $9 \times 10^9/L$ at screening), and platelets of $95 \times 10^9/L$ (as compared to $133 \times 10^9/L$ which was slightly below normal range). Bacterial culture in bronchial samples was positive for *Staphylococcus aureus*, *Pneumococcus* and *haemophilus influenza*. A further bacterial culture grew *Enterobacter cloacae*. **Aspiration pneumonia** was suspected. In addition to multiple antibiotics treatment, the patient received IV MP and 6 sessions of **plasmapheresis** (b) (6) which led to partial recovery of motor strength, but difficulty in swallowing and respiratory distress persisted.

On (b) (6) she presented hypovolemia and cardiocirculatory arrest requiring resuscitation. A bronchioalveolar lavage grew *Stenotrophomona maltophilia* and **cytomegalovirus** (viral load 2552 copies). On Day 202 she died of **septic shock and multiorgan failure**. The investigator considered the infection to be a complication of MS and aspiration pneumonia because of swallowing difficulties. No autopsy is available.

Reviewer Comment: This 37 year-old subject had 2 MS relapses within 3 years prior to entering the trial. After discontinuing DAC HYP for a cutaneous reaction the patient had a severe MS relapse that did not respond to MP. She was treated with plasmapheresis but had persistent respiratory distress related to MS and/or superimposed infection. Her EDSS went from 3.5 to 10 (death). The cause of death was suspected to be aspiration pneumonia. The palmo-plantar eczema which started approximately one month before the death appears to be unrelated to the episode of respiratory distress/sepsis, however, the event had not fully resolved at the time or respiratory distress. BAL cultures grew several organisms, including CMV. It is unclear to me whether this was severe MS complicated with aspiration pneumonia or there was some other ongoing underlying infection. The role of DAC HYP on this death cannot be ruled out.

301/744-007, Worsening MS. Aspiration pneumonia, sepsis.

46 year-old female from India started DAC HYP 150 on (b) (6). She had had 2 MS relapses within the prior 3 years. Her last relapse had been on December 2010. Her baseline EDSS score was 4.5. The narrative does not mention results of the baseline MRI. On (b) (6) after 4 doses of DAC HYP 150 (Day 95 of study; most recent dose had been on Day 85) she had dysphagia, loss of consciousness, dyspnea and fever and was hospitalized for SAE of “acute exacerbation of MS involving brain stem (not a relapse)” and aspiration pneumonia. On admission to the hospital she was febrile, unresponsive, and had neck stiffness. A chest x-ray showed bilateral lung consolidation diagnosed as aspiration pneumonia. She had quadriplegia and difficulty swallowing. On (b) (6) MRI showed extensive increased white matter lesions bilaterally and increased cerebral demyelination. While the event was ongoing she received MP (b) (6) azathioprine (b) (6) antibiotics (b) (6) and oxcarbazepine (b) (6). She became conscious and responsive to simple commands but developed quadriplegia and was unable to swallow, requiring a percutaneous endoscopic gastrostomy

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(PEG). The event of MS exacerbation was considered resolved with sequelae on Day 109. She was discharged to home care (b) (6) but the event of aspiration pneumonia was ongoing. On (b) (6) the family withdrew consent for the patient to participate in the study. On (b) (6) (Day 202) another SAE of aspiration pneumonia was reported, along with decubitus ulcer and sepsis. She died of cardiorespiratory arrest. As per the patient profile she received DAC HYP on Day 1, 29, 57 and 85 of study 301. No autopsy is available.

Reviewer Comment: The narrative submitted for this patient is confusing (as many other narratives in the DAC HYP development program). I have attempted to integrate the information from the narrative and the CRF, as well as from the patient profile submitted on 4/2/15 and the graphic patient profile generated by Empirica Study. The full narrative for this patient as submitted by the applicant is included in Section 13.3.2 of this review.

It is likely that this patient had aspiration pneumonia because of MS relapse/progression. The supplemental information included in the narrative states that the relapse involved the brainstem. It is unclear whether the patient had brainstem involvement prior to starting DAC HYP. She may also have had an ongoing infectious process before the episode of MS exacerbation. On the first admission to the hospital she was febrile, unresponsive, with "neck stiffness" but there is no mention of work up for meningitis or encephalitis. It appears that the quality of the acute exacerbation of MS was different from previous episodes because in addition to high dose IV MP she was started on azathioprine right away. The patient was discharged to home care but the event of aspiration pneumonia never resolved and was eventually complicated with fatal sepsis. Immunosuppression by DAC HYP and azathioprine may have influenced the fatal outcome of the infection. The role of DAC HYP on this death cannot be ruled out.

303/537-012. Fall. Subdural hematoma.

39 year old female, received 30 doses of DAC HYP 150 in study 301 and 8 doses in study 303 (First day on 303 was (b) (6); last dose was on (b) (6), week 24 of study 303). As per the narrative, on day 184 the patient had diarrhea and weakness. Two or three days later she fell in the bathroom and was admitted to the hospital in coma. A head CT showed acute subdural hematoma in the left hemisphere. She reportedly developed cerebral edema and died. As per the patient profile, during study 301 the patient presented elevated ALT/AST but it resolved in study 303. On Day 156 she presented AE of lymphadenopathy, reactive lymphocytosis and lymphoproliferative disorder; on Day 183 she had venous thrombosis of the lower leg, which was treated with heparin. None of these events was serious. There is no information about the lymphoproliferative disorder, which is likely related to DAC HYP. The patient fell on Day 191 (SAE) and died on Day 193 of subdural and subarachnoid hemorrhage with brain edema and compression of the ventricular system. Laboratory data on weeks 12 and 24 showed lymphopenia (0.8×10^9 /L) and atypical lymphocytes (1-2%). Serum DAC antibodies were negative at all visits.

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Reviewer Comment: this patient fell and died of a traumatic intracranial bleeding 3 ½ years into DAC 150 treatment, after being treated with heparin because of venous thrombosis preceded by diarrhea and lymphoproliferative disorder. Patients with MS are at increased risk of DVT. However, the role of DAC HYP in this death cannot be ruled out.

In summary, five deaths occurred in patients treated with DAC HYP, all female ages 39 to 49 years; four on DAC HYP 150 and one on DAC HYP 300, among a total of 2236 patients with MS exposed to DAC HYP. Two deaths were related to study drug (one autoimmune hepatitis and one infectious complication of a serious cutaneous reaction after discontinuing drug because of elevated liver enzymes). The case of autoimmune hepatitis occurred after re-starting DAC, following a 6 month washout period. The patient received one dose of DAC HYP when ALT was 12x ULN and corticosteroid treatment was started too late.

DAC HYP may have played a role in the other 3 deaths. Two patients with MS relapse died of aspiration pneumonia and sepsis within 3 months after the last dose of DAC HYP in study 301. One of them had discontinued treatment because of eczema; the other had discontinued because of MS relapse which had been treated with IV MP and azathioprine. Aspiration pneumonia may occur in patients with advanced MS but DAC HYP may have played a role by decreasing the subjects' ability to fight these infections, leading to an unfavorable outcome. Moreover, biologic agents are known to induce autoimmune diseases including neurologic autoimmunity. It is impossible to distinguish whether these MS relapses were induced by DAC HYP or part of the underlying disease. The fifth patient who died in the DAC HYP treatment group did so after a fall at home with head trauma and acute subdural hematoma. She had been diagnosed with lymphoproliferative disorder and deep venous thrombosis, and was receiving heparin at the time of the fall.

Five deaths occurred in patients treated with IFNβ1a (as described in Table 10, 3 of which occurred beyond 30 days after the last dose. None of them appears to be directly related to study treatment.

Subsequent to the fatal cases of autoimmune hepatitis and infectious complication of a cutaneous reaction, the protocols were amended to expand exclusion criteria and include stricter liver enzyme monitoring. No further deaths occurred because of liver or skin disease. It is unclear whether the possibility of receiving treatment when the drug should have been withheld could happen in the postmarketing setting if patients self-inject without a healthcare provider's supervision.

8.4.2. Serious Adverse Events

The most commonly reported SAE in both controlled studies was MS relapse. Excluding MS relapse, the overall risk of SAEs was greater in the DAC groups as compared to placebo (7%, 9% and 6%, in the DAC HYP 150, DAC HYP 300 and placebo groups, respectively) and in the DAC HYP 150 group as compared to IFNβ1a/IFNβ1a (16% and 10%, respectively). Tables of SAE by MedDRA SOC up to 180 days after last dose are presented below for the controlled studies as generated by this medical officer using Empirica Study, with the caveat that some may have been missed because of miscategorization of AE seriousness.

Table 11. DAC HYP BLA. Patients with Serious AEs by MedDRA SOC. Study 201.

PATIENTS WITH SAE MEDDRA SYSTEM ORGAN OR CLASS	Placebo N=204		DAC 150 N=207		DAC 300 N=208	
	n	%	n	%	n	%
ANY SAE	53	26.0	32	15.5	36	17.3
ANY SAE EXCLUDING MS¹	12	5.9	15	7.2	18	8.7
INFECTIONS AND INFESTATIONS	0	0.0	6	2.9	3	1.5
GASTROINTESTINAL DISORDERS	1	0.5	3	1.4	2	1.0
HEPATOBIILIARY DISORDERS	1	0.5	2	1.0	1	0.6
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	0	0.0	2	1.0	3	1.4
EYE DISORDERS	0	0.0	1	0.5	0	0.0
INJURY, POISONING AND PROCEDURAL INVESTIGATIONS	2	1.0	1	0.5	0	0.0
NEOPLASMS BENIGN, MALIGNANT AND	0	0.0	1	0.5	0	0.0
PSYCHIATRIC DISORDERS	1	0.5	1	0.5	2	1.0
REPRODUCTIVE AND BREAST DISORDERS	0	0.0	1	0.5	0	0.0
NERVOUS SYSTEM DISORDERS	2	1.0	1	0.5	2	1.0
NERVOUS SYSTEM EXCEPT MS ¹	45	22.1	20	9.7	22	10.6
BLOOD AND LYMPHATIC SYSTEM DISORDERS	1	0.5	1	0.5	4	2.0
CARDIAC DISORDERS	1	0.5	0	0.0	1	0.5
ENDOCRINE DISORDERS	2	1.0	0	0.0	1	0.5
IMMUNE SYSTEM DISORDERS	1	0.5	0	0.0	1	0.5
METABOLISM AND NUTRITION DISORDERS	0	0.0	0	0.0	1	0.5
MUSCULOSKELETAL AND CONNECTIVE	1	0.5	0	0.0	0	0.0
PREGNANCY, PUERPERIUM AND PERINATAL	1	0.5	0	0.0	0	0.0
RENAL AND URINARY DISORDERS	0	0.0	0	0.0	1	0.5
RESPIRATORY, THORACIC AND MEDIASTINAL	1	0.5	0	0.0	0	0.0
VASCULAR DISORDERS	0	0.0	0	0.0	1	0.5

N= safety population. n= number of patients with events. Source: Generated by FDA Medical Officer using Empirica Study from AE datasets submitted May 14, 2015. One patient may have more than one event but is counted once within each SOC.

¹ Patients with events except MS/MS relapse calculated from AE datasets using JUMP, by excluding the following preferred terms: multiple sclerosis, multiple sclerosis relapse and progressive multiple sclerosis.

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Table 12. DAC HYP BLA. Patients with Serious AE by MedDRA SOC, Study 301

PATIENTS WITH SAE BY MEDDRA SYSTEM, ORGAN OR CLASS	IFN N=922		DAC 150 N=919	
	n	%	n	%
ANY SAE	194	21.0	221	24.1
ANY SAE EXCLUDING MS¹	87	9.4	142	15.5
INFECTIONS AND INFESTATIONS	15	1.6	40	4.6
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS)	11	1.2	14	1.5
NERVOUS SYSTEM	131	14.2	109	11.9
NERVOUS SYSTEM EXCEPT MS ¹	7	0.8	14	1.5
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	7	0.8	43	4.7
BLOOD AND LYMPHATIC SYSTEM DISORDERS	2	0.2	12	1.4
GASTROINTESTINAL DISORDERS	6	0.7	11	1.2
INJURY, POISONING AND PROCEDURAL	8	0.9	9	1.2
HEPATOBIILIARY DISORDERS	4	0.4	7	0.8
PSYCHIATRIC DISORDERS	8	0.9	6	0.7
MUSCULOSKELETAL AND CONNECTIVE TISSUE	3	0.3	6	0.7
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	1	0.1	6	0.7
SURGICAL AND MEDICAL PROCEDURES	2	0.2	5	0.5
RENAL AND URINARY DISORDERS	2	0.2	4	0.4
VASCULAR DISORDERS	2	0.2	4	0.4
METABOLISM AND NUTRITION DISORDERS	0	0	4	0.4
CARDIAC DISORDERS	5	0.5	3	0.4
PREGNANCY, PUERPERIUM AND PERINATAL	4	0.4	3	0.5
INVESTIGATIONS	3	0.3	3	0.3
REPRODUCTIVE SYSTEM AND BREAST DISORDERS	3	0.3	3	0.3
GENERAL DISORDERS AND ADMINISTRATION SITE	1	0.1	3	0.4
ENDOCRINE DISORDERS	1	0.1	1	0.1
IMMUNE SYSTEM DISORDERS	1	0.1	1	0.1
CONGENITAL, FAMILIAL AND GENETIC DISORDERS	0	0	1	0.1
EAR AND LABYRINTH DISORDERS	0	0	1	0.1
EYE DISORDERS	0	0	1	0.1

Source: FDA MO analysis using Empirica Study. .One patient may have more than one event but is counted once within each SOC. ¹ Patients with events except MS/MS relapse calculated from AE datasets using JUMP, by excluding the following preferred terms: multiple sclerosis, multiple sclerosis relapse, progressive relapsing multiple sclerosis and relapsing-remitting multiple sclerosis.

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Other than MS relapse, the most commonly reported SAEs in both studies were in the Infectious and infestations SOC. In 201, SAE of infections and Skin reaction occurred only in the DAC groups (overall 2.1% and 1.2% of patients, respectively as compared to none on placebo). After infections, the most common SAE in study 201 were in the Gastrointestinal, Skin and subcutaneous tissue, and Nervous system disorders SOCs; in study 301 the second most common SAE was in the Neoplasms SOC, but the incidence of neoplasms was similar on DAC and IFNβ1a. Other SAE with incidence greater than 1% in any treatment group were in the Skin and subcutaneous tissues disorders SOC (1.5% and 0.1% respectively), Nervous system disorders other than MS (1.5% and 0.9%, respectively), Blood and lymphatic system disorders (1.4% and 0.2 % respectively) and GI disorders (1.2% and 0.7%, respectively).

Reviewer Comment: DAC is associated with an increased risk of serious infections, hematologic, skin, GI and liver related events as compared to placebo and IFNβ1a. Overall, there is no evidence of a dose response in terms of SAE between DAC150 and 300 in study 201. See further discussion under individual AE categories.

SAE in the Total DAC HYP database by SOC.

As discussed earlier, the Total DAC database includes the two controlled studies and their extensions, as well as study 302. The database does not allow adequate evaluation of dose response; therefore, tables in this review show analyses for the pooled Total DAC experience. SAE in the Total DAC database up to 180 days after last dose as of the SUR are summarized below.

Table 13. Patients with SAE by MedDRA SOC in the Total DAC database, SUR

PATIENTS WITH SAE BY MedDRA SYSTEM, ORGAN OR CLASS	Total DAC N=2236 (5214 PYRs)	
	n	%
Patients with ANY SAE	539	24.1%
Patients with ANY SAE EXCEPT MS/MS RELAPSE¹	352	15.7%
INFECTIONS AND INFESTATIONS	99	4.4
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS)	30	1.3
NERVOUS SYSTEM	274	12.3
NERVOUS SYSTEM EXCEPT MS*	31	1.4
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	44	2.0
GASTROINTESTINAL DISORDERS	35	1.6
BLOOD AND LYMPHATIC SYSTEM DISORDERS	30	1.3
INJURY, POISONING AND PROCEDURAL	26	1.2
HEPATOBIILIARY DISORDERS	23	1.0

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PATIENTS WITH SAE BY MedDRA SYSTEM, ORGAN OR CLASS	Total DAC N=2236 (5214 PYRs)	
	n	%
PSYCHIATRIC DISORDERS	16	0.7
MUSCULOSKELETAL AND CONNECTIVE TISSUE	16	0.7
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	13	0.6
REPRODUCTIVE SYSTEM AND BREAST DISORDERS	11	0.5
INVESTIGATIONS	11	0.5
GENERAL DISORDERS AND ADMINISTRATION SITE	9	0.4
SURGICAL AND MEDICAL PROCEDURES	8	0.4
RENAL AND URINARY DISORDERS	8	0.4
VASCULAR DISORDERS	8	0.4
METABOLISM AND NUTRITION DISORDERS	6	0.3
CARDIAC DISORDERS	6	0.3
IMMUNE SYSTEM DISORDERS	5	0.2
PREGNANCY, PUERPERIUM AND PERINATAL	4	0.2
ENDOCRINE DISORDERS	4	0.2
EAR AND LABYRINTH DISORDERS	3	0.1
EYE DISORDERS	3	0.1
CONGENITAL, FAMILIAL AND GENETIC DISORDERS	1	<0.1

Source: MO analysis. JUMP ADAE3 SUR. *MS/MS relapse includes multiple sclerosis, multiple sclerosis relapse and progressive multiple sclerosis. Includes patients receiving alternative MS medications.

In general, the incidence of SAE by body system in the Total DAC HYP experience was in line with that of DAC HYP 150 in study 301. Overall, 28% had a SAE, including 14% with SAE in the Nervous system disorders SOC (1.4% for nervous system except events reported as MS/MS relapse/progressive MS). A total of 17% of patients had SAE outside the nervous system disorders SOC. Most common SAE other than MS were infections, skin, GI and Blood and lymphatic disorders. For additional discussion see review by SOC and preferred term, below.

Serious Adverse Events by SOC and Preferred Term

This section discusses SAE in controlled studies and the Total DAC HYP database by SOC in alphabetical order and includes summary tables for the Total DAC HYP database. (Tables for the individual studies are presented in Appendix 13 (13.3.3) of this review). Selected narratives are presented after the tables. In general, narratives for patients with SAE on placebo or IFNβ1a are not included.

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- **Patients with SAE in the Blood and lymphatic system Disorders SOC**

In study 201, one SAE of lymphadenitis was observed in study 201 in the DAC150 group, as compared to none on placebo. In study 301 there were nine SAE of lymphadenopathy/ lymphadenitis/lymphoid tissue hyperplasia (L/L/L) in the DAC150 group (1%) as compared to none on IFNβ1a. Analyses of blood and lymphatic events in the Total DAC experience as of the SUR are shown below.

Table 14. Patients with SAE in the Blood and lymphatic system Disorders SOC, Total DAC, SUR

SOC/PT	Total DAC N=2236		With cases AFTER SUR CUT-OFF N=2236
	n	%	
ANY	30	1.3	49 (2.2)
AGRANULOCYTOSIS	1	0.0	
ANAEMIA	2	0.1	
HEMOLYTIC ANEMIA			3 (0.1)
HISTIOCYTOSIS HAEMATOPHAGIC	1	0.0	
IRON DEFICIENCY ANAEMIA	2	0.1	
LEUKOPENIA	1	0.0	
LYMPHADENITIS	7	0.3	
LYMPHADENOPATHY	12	0.5	27 (1.2)*
LYMPHOID TISSUE HYPERPLASIA	1	0.0	
LYMPHOPENIA	2	0.1	
PERNICIOUS ANAEMIA	1	0.0	
THROMBOCYTOPENIA	3	0.1	4 (0.2)

Source: Medical Officer JUMP analysis ADAE3 datasets submitted with SUR (cut-off November 2014). Does not include additional cases of lymphadenopathy/lymphadenitis/lymphoproliferative disease and three of hemolytic anemia (2 were reported after the cut-off of the SUR; one was diagnosed after 180 day followup but the symptoms started 4 months after last dose, within the 180 day fu period). * Includes 2 non-Hodgkin Lymphoma and 1 sarcoidosis.

At the time of the SUR (cut-off of November 2014), 20 patients had SAE of lymphadenopathy/ lymphadenitis/lymphoid (L/L/L) tissue hyperplasia. As per a response to an FDA request for information for follow up of cases of lymphadenopathy submitted on 7/29/15, fourteen additional cases were reported after the cut-off date of the SUR, mostly from studies 203 and 303, with exposure longer than 3 years, including 2 Non-Hodgkin’s lymphomas (NHL). One more case of lymphadenopathy was submitted on January 29, 2016 (303/622-106*, MFR# 2016BI00176395). There is little information about this case but the patient was suspected of having sarcoidosis and was hospitalized for further workup.

Brief narratives of selected SAE in the Blood system disorders in patients taking DAC HYP are presented below. Additional narratives are presented in Appendix 13. (13.3.7) of this review.

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301/437-001. ANAEMIA, LYMPHADENOPATHY

46 F, mild anemia from the beginning of the trial; SAE of anemia from Day 85 to 96. During the trial she had intermittent pruritus, arthralgia and “infusion related reaction” (Day 222 to 365). Concomitant meds at the time of the event were iron, fluoxetine, and methylprednisolone. On Day 531 generalized lymphadenopathy leading to drug withdrawal; the event was reported as serious 3 weeks later, and resolved almost 6 months later. Ultrasound showed posterior cervical and right subclavicular lymphadenopathy “of inflammatory type.” Tomodensitometry showed many bilateral, basal, pulmonary, parenchymatous micronodules, with some of them calcified and atypical; unusual calcifications of the tracheobronchial cartilaginous rings and hypodense hepatic lesions. On (b) (6), positron emission tomography/computed tomography (PET/CT) scan showed marked hypermetabolism of supra- and subdiaphragmatic lymph nodes. Excision bx of spinal lymph node showed “benign lymphoid hyperplasia.” Laboratory showed low Hb throughout the study with no evidence of abnormal WBC or lymphocyte count. The last dose of DAC HYP was in (b) (6). Lymphadenopathy was considered resolved (b) (6) although lymph nodes were still visible with ultrasound (b) (6). *This appears to be benign lymphoid hyperplasia. However, it is associated with intermittent pruritus and arthralgia, with lung micronodules and heterotopic calcifications suggestive of sarcoidosis. Workup was incomplete to adequately rule out immune mediated diseases.*

203/505-032* LYMPHADENOPATHY

49F. Lymphadenectomy almost 5 years into treatment with the study drug. Concom: fluoxetine. Hospitalized (b) (6) for lymphadenectomy. Histopathology showed lymph nodes with blurred histoarchitecture, with maintained reproduction centers, and with presence of some Hodgkin-like cells (not numerous). The study drug was stopped temporarily. As per follow up pathology report, picture does not allow a diagnosis of lymphoma; it corresponds to reactive changes, “probably with a background of toxoplasmosis” although serology for Toxoplasmosis (IgM) was negative. The patient is not being treated and is being followed by the site. *Drug discontinued. Event ongoing at time of last follow up. Also incomplete workup for evaluation of immune mediated diseases. Unclear where the diagnosis of toxoplasmosis came from.*

303/609-013* LYMPHADENOPATHY (also exfoliative rash, edema, lung nodules)

39 M. This case was reported as non-serious LN leading to drug WD in the ISS, but in a subsequent follow up it was considered a SAE. First report of lymphadenopathy was in June 2014. Event occurred after 40 doses of DAC 150 (33 in study 301 and 7 in study 303). Hospitalized for generalized exfoliative rash (b) (6). LN was located in right axilla and supraclavicular fossa, lateral wall of right chest and near nape of the neck. Fine needle aspirate suggested reactive lymphadenopathy. CT of chest showed nodules (6-7 mm diameter) disseminated bilaterally in **pulmonary**

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interstitium, peripheral and subpleural portions and along interlobar fissures. Few lymph nodes up to 15 mm were visualized in the **mediastinum**. Liver enlargement without lesions was also noted. She also was hospitalized for event of peripheral edema [REDACTED] (b) (6). Dx on admission was generalized lymphadenopathy, generalized eczema and suspected paraneoplastic syndrome. DRESS was considered in the differential diagnosis. Abd US numerous **lymph nodes in the region of the hepatic hilum** and along the aorta and multiple varicose-type veins along the left iliac vessels. Bronchoscopy and cultures were negative for TB and malignancy. Lymphadenopathy was considered "resolved with sequelae" [REDACTED] (b) (6). *In my opinion this is consistent with sarcoidosis.*

203/906-005.* 49 F had received 67 cumulative doses of DAC HYP 150 mg. On Day 2005 of DAC treatment, (44 days after her most recent dose of DAC HYP), the subject was hospitalized for SAE of nasal hemorrhage and hemorrhagic rash on both legs due to suspected hemorrhagic vasculitis. Upon admission to the hospital, her hemoglobin was 92 g/L; platelets were not reported. Abdominal ultrasound showed splenomegaly. Her treatment included prednisolone and etamsilate. On Day 2009, the hematologist confirmed the final diagnosis as **thrombocytopenic purpura and post hemorrhagic anemia** and considered them related to study drug. DAC had previously been interrupted because of an acute respiratory viral infection, and was now permanently discontinued. The subject was discharged from the hospital, and the events of thrombocytopenic purpura and post hemorrhagic anemia "were considered resolved" on Day 2014. The subject withdrew from the study. *Although reported as resolved, it is unclear for how long the patient required corticosteroid treatment or if she was able to get off CS at all.*

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SAE of Lymphadenopathy

Overall, there were at least 35 SAE of L/L/L among 2236 patients who received DAC HYP (1.6%) as of January 2016, 15 of which were reported following the cut-off for analyses of the SUR. DAC HYP was clearly associated with increased risk of SAE of L/L/L as compared to IFN β 1a in study 301 (1% vs. 0, respectively).¹¹

Most of the patients with SAE of L/L/L had a brief hospitalization for diagnostic procedures. Some had long or recurrent hospitalization, when systemic diseases (tuberculosis, malignancy) were suspected. Onset of lymphadenopathy occurred throughout the study. Most SAE of lymphadenopathy led to drug withdrawal. As of the SUR, 14 of 20 were reported as drug withdrawn. Some of these cases remain “unresolved.”

Among the patients who had a biopsy or fine needle aspiration (FNA), pathology was mostly consistent with benign reactive hyperplasia. However, a relatively small number of patients had a biopsy and/or fine needle aspiration (301/477-005, 301/678-008, 303/613-009, 205-004, 301/614-037, 622-009, and 609-013). *Total number of patients who underwent these procedures is not known. FNA may miss pathologies such as lymphoma and sarcoidosis.*

Five of the SAE identified in the database were related to an infectious process (peritonsillar abscess, folliculitis, EBV infection, CMV, tuberculosis). Some additional cases may have been related to some undiagnosed infection.

At least two of the reported SAE of lymphadenopathy were diagnosed as NHL (*two additional cases of NHL were reported without reporting lymphadenopathy*).

Two of the cases of lymphadenopathy are reported to be associated with a “benign salivary neoplasm” (upon an FDA request additional information was submitted but there is no relevant new data about these cases). *I wonder if these could be Sjogren’s syndrome. Salivary gland involvement should have prompted evaluation of antinuclear antibodies [ANA], and if positive, evaluation of SSA and SSB antibodies*).

At least three of the SAE of LN were associated with a skin reaction, one was associated with thrombocytopenia and several were associated with interstitial lung changes suggesting a systemic reaction such as Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) but most were not accompanied by eosinophilia, rash or other organ involvement.

None of the SAE in the Blood disorders SOC was diagnosed as sarcoidosis as of the SUR but it is unclear if any patient had the work up to rule out this diagnosis. There was one SAE of

¹¹ The overall number of all serious and nonserious AE of L/L/L in Total DAC HYP database was 137 cases (6.1%). The analysis of SAE in study 301 shows similar percentage of serious and non-serious AE of L/L/L: 59 (6%) on DAC150, vs. 10 (1%) on IFN.

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pulmonary sarcoidosis and two non-SAE of sarcoidosis NOS in the application at time of the SUR. Six cases of sarcoidosis were reported after the cutoff of the SUR. Sarcoidosis should have been considered in the presence of systemic lymphadenopathy, particularly if associated with hilar lymphadenopathy and lung nodules, as presented by several patients in this application. *For additional cases of sarcoidosis see Section 8.5.3 of this review, Specific Safety issues, Immune-mediated reactions.*

SAE other than lymphadenopathy

Three SAE of immune hemolytic anemia and **five** of thrombocytopenia were diagnosed in this clinical program as of December 2015.

Two of the three cases of hemolytic anemia were reported after the cut-off of the SUR (203/100-002*, 302/463-103*). One patient (301/472-005) was diagnosed with HA 184 days after the last dose of DAC in study 301, (while on alternative MS therapy [IFN]). However, symptoms of anemia started before the 180-day window period. All three required hospitalization and corticosteroid treatment. One of them has been successfully weaned off corticosteroids, the other were ongoing at the time of last follow up. *One of them was discontinued from the study and will not have follow up.*

The five SAE of thrombocytopenia occurred after 4 to 67 doses of DAC. Case 301/480-002 was confounded by use of carbamazepine; 301/670-017 received prednisone 60 mg day and took 7 months to taper off (the SUR states that this patient, with a dummy ID of 3011311 had HIV induced thrombocytopenia); 301/617-003 (had rash, anemia and lymphadenopathy, suspected viral infection treated with 40 mg methylprednisolone,; 303/649-009 (in a patient with AIH during tapering; in a follow up report the applicant stated that the latest patient was successfully tapered off, but the duration of treatment is unclear) and 203/906-005*(presented in the table). Therefore, there are at least of 4 cases of thrombocytopenia that may be related to DAC.

One case of hemophagocytic syndrome (HPS) was reported in this SOC, in association with multiorgan failure “in the setting of septicemia” but in the absence of a clear infectious agent or source (203/303-005). HPS has been reported in the context of sepsis, lymphoma and use of immunosuppressors. Additional information about this case is included in Appendix O (selected narratives of events in the Infections and Infestations SOC.)

There was a case of agranulocytosis in this database (301/660-007). The patient had been recently diagnosed with Reiter’s syndrome (reactive arthritis) and had longstanding skin rash. Agranulocytosis led to drug withdrawal. Agranulocytosis resolved after 2 months. Reiter’s syndrome did not resolve. Agranulocytosis was likely related to treatment with sulfa drugs and unlikely related to DAC HYP but Reiter’s syndrome may have been related to DAC HYP.

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One case of pancytopenia was identified in this database but it is not in the datasets (a patient with suspected brucellosis discussed under Infections). No cases of aplastic anemia were identified in the database.

Because of the effects of DAC HYP on Tregs and NK cells, there is biological plausibility for a role of this product on the events of hemolytic anemia, thrombocytopenia and HPS. In my opinion they are DAC related.

- **SAE in the Cardiac Disorders SOC**

There was no excess of SAE in the DAC groups as compared to placebo or IFNβ1a for the Cardiac disorders SOC. Analyses of patients with SAE events in these SOCS in the Total DAC database are shown below.

Table 15. SAE in Cardiac disorders SOCs, Total DAC HYP, SUR

Pts with AEs	Total DAC N=2236	
CARDIAC DISORDERS	6	0.3
MYOCARDIAL ISCHAEMIA	1	<0.1
MYOCARDIAL INFARCTION	1	<0.1
BRADYCARDIA	1	<0.1
CARDIOMYOPATHY	1	<0.1
PALPITATIONS	1	<0.1
CARDIO-RESPIRATORY ARREST	1	<0.1

MO JUMP analysis, ADAE3, SUR.

There were 2 cases of cardiomyopathy in this application (303/554-007 and 303/433-003*, the later after cutoff of the SUR) and one of cardiorespiratory arrest (301/744-007 in patient who died of MS relapse, aspiration pneumonia and sepsis in study 301) in this database. 303/433-003 was considered by the investigator to be related to drug and is still ongoing. Both cardiomyopathies presented in patients with preexistent risk factors and it is difficult to attribute to daclizumab, although, one of the patients with cardiomyopathy also presented elevated liver enzymes and skin rash. In study 301, the risk of ischemic events with DAC HYP 150 was not higher than with IFNβ1a. Cases of cardiomyopathy are described in Appendix 13.3 of this review (13.3.8).

- **SAE in Congenital, Ear and Labyrinth Disorders SOCs**

There was no excess of SAE in the DAC groups as compared to placebo or IFNβ1a for the Congenital, and Ear and labyrinth disorders SOCs. There were few events in the Total DAC HYP

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database (one dermoid cyst, in the Congenital SOC, unrelated to drug; two of vertigo and one acute vestibular syndrome that may have been manifestations of MS).

- **SAE in Endocrine System disorders SOC**

There was no excess of SAE in the DAC groups as compared to placebo or IFNβ1a in the Endocrine System disorders SOC (one diabetes insipidus on placebo, one autoimmune thyroiditis on DAC 300 in study 201; two of hyperthyroidism [one on IFN, one on DAC] in study 301. There were 2 additional thyroid SAE in the extension studies (hyperthyroidism and Basedow's disease). Additionally 2 cases of diabetes mellitus were coded under the MedDRA Metabolism and nutrition disorders SOC but are appropriate to include in the Endocrine disorders SOC. (*Diabetes may be coded under either SOC, there is no preferred or primary SOC*).

Table 16. Patients with SAE in Endocrine Disorders SOC

	TOTAL DAC	
SOC	N=2236	
PT	n	%
Any patient with event	5	0.2
GOITRE	1	<0.1
AUTOIMMUNE THYROIDITIS	1	<0.1
BASEDOW'S DISEASE	1	<0.1
HYPERTHYROIDISM	2	0.1
DIABETIC KETOACIDOSIS	1	<0.1
DIABETES MELLITUS	1	<0.1

As of SUR. One patient may have more than one event. This table includes one patient with diabetes mellitus reported under the metabolic SOC but not under the endocrine SOC.

An additional case of Type 1 DM was reported after the cutoff of the SUR (303/667-017*).

Brief narratives are shown below. Total DAC HYP database

201/ 752-012	51 F On DAC 300. Developed autoimmune thyroiditis of mild intensity. Final dose of DAC in study 201 (dose #13) was on Day 336. Duration is reported to be from Day 385 to Day 392. No action taken with drug because the treatment was already completed. She did not enter study 202.
301/ 327-005	44 F On DAC 150. She had a medical history of goiter. A non-serious AE of hyperthyroidism was reported on Day 116, after 5 doses of DAC150. She started carbamazepine on Day 129. On Day 150, 10 days after the 6 th dose of DAC150, she complained of palpitations and weakness and was admitted to the hospital with diagnosis of thyrotoxicosis and ketoacidosis (no blood glucose level provided). She was treated with insulin and carbamazepine, and discharged after 4 days on chronic insulin therapy (as of the last follow up

	the event has not resolved). <i>This patient is predisposed to autoimmunity but DAC may have played a role on the worsening of hyperthyroidism and new onset of Type I diabetes. There are no routine measurements of glucose, but there is mention in the profile that the patient had high glucose levels on home blood glucose monitoring. This patient developed colitis in study 303.</i>
202/ 765-003	25 F. Received DAC 300 in 201&202. Basedow’s disease (goiter) of moderate intensity reported during 201. Thyrotoxicosis requiring PTU treatment and thyroidectomy in 202. This patient also was diagnosed with urticaria, chronic autoimmune hepatitis and leukopenia, thought to be related PTU treatment. <i>(Case is discussed in more detail under liver toxicity)</i>
203/ 563-001	48F. Received DAC 150 in studies 201/202/203. She had a “benign neoplasm of thyroid gland” during study 202. Goiter of moderate severity reported in 203. Patient underwent thyroidectomy because of suspected malignancy, but pathology was benign. No action taken with drug because drug already discontinued because of alveolitis, later diagnosed as idiopathic pulmonary fibrosis . <i>(Case is discussed in more detail under respiratory SAEs)</i>
303/ 438-001	52 F at entry to 301. SAE of Diabetes mellitus on Days 14 to 57 of study 303 and “DM inadequate control” from Days 167 to 174. She had received IFNβ1a in 301. During 301 had AE weight increased and high triglycerides but no events of hyperglycemia. As per review of Empirica Study profiles she was already received insulin in study 301 therefore, she had a history of diabetes although DM was not captured in study 301. There are no blood glucose measurements in either study 301 or 303.
303/ 667-017*	A patient with eczema and drug induced liver injury developed Type 1 DM and toxic pancreatitis. Case discussed under Hepatobiliary SOC.

There is an increased prevalence of autoimmune thyroid disease in patients with MS. However, one of the pts with a SAE of hyperthyroidism also developed Type I diabetes mellitus and colitis; another developed idiopathic pulmonary fibrosis and a third was diagnosed with chronic autoimmune hepatitis. One patient who developed Type 1 DM also had an exanthematous maculopapular rash, drug induced liver injury and pancreatitis, which could be consistent with an IPEX-like syndrome. An additional case of rash (granuloma annulare or eczema), pancreatitis and diabetes mellitus was reported as an IND safety report on 3/16/16 (303/667-003). The patient who developed a SAE of hyperthyroidism on IFNβ1a (301/604-142) had no other apparent autoimmune diseases.¹²*

¹² Of note, 22 patients had serious and non-serious adverse events consistent with diabetes mellitus in the Total DAC database under various PTs (diabetes, hyperglycemia, glucose intolerance), under the Investigations or the Metabolic SOCs. Blood glucose was not measured/recorded in these patients. In study 301, 5 and 3 AE were

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Onset of SAE of diabetes and hyperthyroidism occurred 14 to 1190 days into treatment (mean 405 days).

Additionally, subject 201/903-012, a 22 F developed **diabetes insipidus** (Endocrine disorders SOC) in the placebo group in study 201, after nine doses, but the **patient was from site 903** and therefore she was on active treatment (either DAC 150 or 300), not on placebo. Event reported to last from Day 228 to 279. Labs were unremarkable except that platelets and thyrotropin were elevated before entering the study.

It is unclear if it is nephrogenic or central diabetes insipidus (DI). Central DI is caused by hypopituitarism. Assessment requires results of a desmopressin test and pituitary magnetic resonance imaging (MRI). The most common cause is idiopathic but can be immune-mediated (e.g. granulomatous or lymphocytic infiltration; drug-induced, such as in the case of ipilimumab induced hypophysitis). In my opinion it is uncertain but plausible that the event of diabetes insipidus was related to DAC HYP.

- **SAE in the Eye disorders SOC**

In Study 201, 1 of 207 (0.5%) DAC 150 subject compared to none on placebo or DAC 300 had an SAE in the Eye disorders SOC; this was a subject with retinal vein occlusion (the patient who died of sepsis and psoas abscess).

In Study 301, 1 of 919 (0.1%) DAC 150 subjects compared to none on IFN had a SAE in this SOC; that was cystoid macular edema. In the total DAC database, there was one SAE of choroiditis, which is more common in patients with inflammatory diseases such as MS than the general population. Therefore, it is difficult to attribute to daclizumab.

A 15-day report of recurrent Iritis was submitted in October 2015 (303/609-008) approximately one and half years after initiation of DAC150 therapy. At the time of the event she also had hypothyroidism. The study drug was discontinued. The investigator considered the event related to study drug. *Iritis could be a manifestation of autoimmunity. It is unclear if the hypothyroidism developed during study 303, study 301 or earlier.*

- **SAE in the GI disorders SOC**

There was a slight imbalance of total number of SAE in this SOC in subjects on DAC (1.4% on DAC 150, 1% on DAC 300) compared to placebo (0.5%) in study 201. This included 1 case of Crohn's' disease on DAC 300 (0.5%) that did not occur on placebo or DAC150. There was also a

reported under these PTs in the DAC and IFN groups, respectively. In study 301, 24 and 22 patients had some thyroid disorder (hypothyroidism, hyperthyroidism, goiter).

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slight imbalance in the number of events in the DAC 150 group (11/919, 1.2%) as compared to INFβ1a (6/ 922, 0.7%). Of note, there was one case of ulcerative colitis, one colitis and one enterocolitis in the DAC 150 group as compared to none on IFNβ1a. The excess of SAE of colitis on DAC150 is consistent with the analyses of all serious and non-serious GI AE in this study.¹³

In the Total DAC experience there were 35 (1.6%) subjects with SAE in the GI disorders SOC, including 12 cases with colitis (see table below).

Table 17. SAE in Gastrointestinal Disorders SOC, Total DAC HYP database, SUR

Table 16.c, Total DAC experience SOC/PT	Total DAC N=2236	
	n	%
ANY	35	1.6
ABDOMINAL PAIN/ABDOMINAL PAIN UPPER	3	0.1
ANAL FISTULA	1	<0.1
APHTHOUS STOMATITIS	1	<0.1
COELIAC DISEASE	1	<0.1
COLITIS	2	0.1
COLITIS ISCHAEMIC	1	<0.1
COLITIS MICROSCOPIC	1	<0.1
COLITIS ULCERATIVE	6	0.3
CROHN'S DISEASE	2	0.1
DIARRHOEA	3	0.1
ENTEROCOLITIS/ENTEROCOLITIS HAEMORRHAGIC	2	0.1
GASTRIC DISORDER	1	<0.1
GASTRITIS/GASTRITIS EROSIIVE/GDUODENITIS	4	0.2
GASTROOESOPHAGEAL REFLUX DISEASE	1	<0.1
HAEMORRHOIDS	1	<0.1
ILEUS	1	<0.1
INGUINAL HERNIA	2	0.1
NAUSEA/VOMITING	2	<0.1
OBSTRUCTION GASTRIC	1	<0.1
PANCREATITIS	1	<0.1

MO JUMP analysis. ADAE3 datasets. SUR. One more case of Crohn's was reported after cutoff of the SUR.

Selected narratives are presented below. Additional listings and narratives are included in Appendix 13 of this review (13.3.9).

¹³ In study 301, a total of 14 patients had serious and nonserious AE of consistent with inflammatory colitis including colitis (n=4), microscopic colitis (2), enteritis (n=4), and one case each of colitis ulcerative, inflammatory bowel disease, proctitis, proctocolitis, in the DAC150 group as compared to none on IFNβ1a.

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Selected SAE in GI disorders SOC

201/454-007. CROHN'S DISEASE

22 M. Severe. Diagnosed on Day 354, after 12 doses of DAC300 in study 201 ("no action was taken with drug" but patient did not enter study 202). Symptoms of enterocolitis started approximately 1 ½ months prior to diagnosis. Colonoscopy showed pancolitis and terminal ileitis. Treated with folic acid, Cipro, mesalazine, metronidazole, prednisone, sulfasalazine and later azathioprine. Alternative treatment started with azathioprine for Crohn's disease. Event is considered ongoing, *Not resolved as of the SUR.*

203/505-026. COLITIS ULCERATIVE

53 F. She received DAC 150 in 201; Placebo/DAC 150 in 202; DAC 150 in 203. Ulcerative colitis was diagnosed on Day 823 of study 203 (Day 1551 of DAC, after 50 doses of DAC). The patient had recurrent hemorrhagic diarrhea and episodes of colitis since Day 540 of study 203. Drug was interrupted twice before it was withdrawn because of colitis. The last dose of DAC150 was on Day 815 of study 203. During a second hospitalization WBC was 16,000, she had anemia, low albumin, low potassium, elevated CRP, high platelet count. Treated with hydrocortisone, oral methylprednisolone, metronidazole, meropenem mesalazine and fluids. Condition deteriorated with increased edema of the legs, ascites and hydrothorax. Colonoscopy was consistent with ulcerative colitis. Abdominal CT showed fluid in the left pleural cavity, numerous enlarged retroperitoneal lymph nodes, ascites and an abscess in the process of formation. Treatment included electrolyte replacement, 1 unit of fresh frozen plasma and 2 units of packed RBCs and oral methylprednisolone. On study Day 856 of study 203, the subject was discharged from the hospital, and the event was considered resolved with sequelae of hypokalemia, hypoalbuminemia, and anemia. *It is unclear for how long mesalazine and corticosteroids were required.* On Day 867 of study 203 (52 days after last dose of DAC) she was hospitalized for deterioration of neurologic condition. Labs showed hematocrit of 31%, elevated CRP, low potassium. She was discharged from the hospital on study day 875 in "stable general and neurological condition" and the event was considered resolved. *Stopping MS treatment may leave patient susceptible to MS relapse.*

303/611-012 COLITIS ULCERATIVE. 29 M. Received IFNβ1a in 301. Patient was hospitalized for a few days for diarrhea, fever and body weight loss, after 14 doses of DAC HYP. Drug was withdrawn. Biopsy of the small and large intestine showed inflammatory changes consistent with UC. MRI of abdomen showed changes in the small intestine consistent with Crohn's disease. Another bx showed severe active chronic duodenitis with complete villi atrophy consistent with celiac disease. Treatment included metronidazole, hydrocortisone, fluconazole. He was further hospitalized for 10 days in the GI department for further evaluation. Labs showed positive ANA 1:100 and positive pANCA. Other autoABs were negative. Another colonoscopy was consistent with UC. Treatment with sulfasalazine was started. The event was considered related to the suspect drug. The event was considered resolved with sequelae in (b) (6) (6 months after the last dose). *Complex case, patient very sick, required several diagnostic procedures, diagnosed as UC and celiac disease. Unclear how long patient required sulfasalazine.*

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303/141-008. CELIAC DISEASE

34 M. Patient received 36 doses of DAC150 mg in study 301 and 2 doses in study 303. Dx of celiac disease made on Day 1093 to 1233 of DAC treatment (total of 34 doses). Drug was withdrawn. In study 301 had presented maculopapular rash, intermittent mild elevation of ALT and amylase and weight loss. The first dose in 303 (study Day 1) was on Day 1037 of DAC; the second dose was on Day 29 of study 303. On Day 57 of study 303 **ALT was 10xULN, AST 7x ULN**, GGT and ALKP also elevated. Total BR normal. This was the early termination visit. On Day 140 he had duodenal biopsy which along with serology was consistent with celiac disease. The patient was diagnosed as having “**celiac disease causing elevated liver function studies and weight loss.**” Evaluation of potential causes of liver enzyme elevation showed a positive ANA (1:40 speckled) but negative liver autoantibodies and hepatitis serology. Serology was positive for EBV (IgG and IgM) and VZA (IgG and IgM). A liver biopsy showed mostly steatosis with some degree of fibrosis. Events of celiac disease and elevated liver enzymes were considered resolved (b) (6) although ALT remained >1.5xULN until the last available visit. By December 2014 the tissue transglutaminase antibody was still positive but all symptoms had improved since starting the gluten-free diet in June 2014. *Complex case of celiac disease and potential EVB and VZA reactivation, diagnosed in study 303 but significant weight loss started in 301. It is conceivable that DAC HYP increased the risk of developing celiac disease. In isolation, one case of celiac disease does not appear to be related to DAC but in addition to this SAE, three non-serious cases of celiac disease were reported in this application (for whom there is no narrative).*

Excluding the case of ischemic colitis secondary to mechanical compression by psoas abscess (201/304-006, described under Deaths) and one case of enterocolitis that was highly confounded, **12 patients had SAE consistent with inflammatory colitis** (6 ulcerative colitis [202/502-006, 203/505-026, 203/506-012, 203/758-028, 301/453-038 and 303/611-012], 2 Crohn’s disease [201/454-007 and 203/759-006], 2 colitis [203/505-011 and 303/606-010], 1 colitis microscopic [301/156-003], one enterocolitis hemorrhagic [203/556-001] in the DAC HYP database. They were 7 females, 5 males, age 19 to 53 years. Two occurred while on the DAC300 group and, 11 while on DAC150. Patients had received 7 to 50 doses of DAC at the time of the diagnoses. Diagnoses were made > 6 months to up to 52 months since start treatment. Some patients had abdominal symptoms (e.g. non-SAE of colitis) before the event was determined to be a SAE. For instance, patient 203/505-026 was diagnosed with Ulcerative Colitis on Day 1551 (almost 4 years since starting DAC), but had episodes of recurrent bloody diarrhea for approximately 10 months before the diagnosis.

Treatment of colitis, ulcerative colitis, Crohn’s disease included standard therapy for these conditions (sulfasalazine, mesalazine, antibiotics, budesonide for microscopic colitis); but at least 4 patients required IV and/or oral corticosteroid [201/454-007, 202/502-006, 203/505-011]) some of whom also received azathioprine.

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As per the datasets, 4 were withdrawn but per review of the narratives additional patients stopped treatment for various reasons. Some patients continue to receive drug for a few doses but eventually discontinued. At least two patients had two serious episodes. As per the ISS datasets at the time of the SUR, of 12 SAE of inflammatory colitis, seven were reported as “not resolved” and 8 reported no outcome including one patient who was lost to follow up. Even for the resolved cases it is unclear for how long they needed immunosuppressive treatment and if they were able to get off immunosuppression without recurrence.

Some of these patients with colitis and the patient with celiac disease become very sick, requiring prolonged or recurrent hospitalizations and invasive procedures such as duodenoscopy, sigmoidoscopy and colonoscopy with biopsies (occasionally more than once; patient 203/505-026 had at least 2 colonoscopies). Some of the hospitalized patients required hydration and electrolyte replacement. At least 2 cases of colitis required a blood transfusion. At least one patient required frozen plasma, suggesting need for coagulation factors. The patient with celiac disease underwent GI endoscopies and a liver biopsy. Narratives are in Appendix 13.3 of this review.

An additional case of Crohn’s was reported as 15-day safety report after the cut-off of the SUR. Additionally, I have identified two SAE of “C difficile colitis” that on review appear to be non-infectious inflammatory colitis (203/501-013 and 303/622-016 discussed under infections).

Approximately half of these cases of inflammatory colitis were considered by the investigator to be related to DAC. In my opinion all these cases are potentially consistent with DAC HYP induced immune mediated colitis.

Other potentially Immune mediated SAE events in this SOC include celiac disease (described above), pernicious anemia (303/439-007, diagnosed on Day 176 in a patient with atrophic autoimmune gastritis as seen on fundal biopsy). One SAE of acute pancreatitis (303/613-005) was reported in this application. The event resolved but as per Empirica Study patient graphic profile, the patient developed diabetes mellitus (event is not in the datasets). Additional cases of pancreatitis occurred but were not reported as SAE. For additional discussion see Section 8.5.3 of this review, Analyses of submission Specific Safety issues, Immune mediated disorders.

- **General Disorders and Administration site Conditions SOC**

There were no SAE in this SOC in study 201. One case of multiorgan failure, one of asthenia and one of chest pain were reported on DAC 150 in study 301. One SAE of flu-like symptoms was reported among 922 patients receiving IFNβ1a in study 301. SAE in this SOC are summarized below for the Total DAC HYP experience treated patients as of the SUR.

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Table 18. SAE in General Disorders and Administration site conditions SOC. Total DAC HYP SUR

	Total DAC N= 2236	
	n	%
Any SAE in this SOC	9	0.4 %
Influenza like illness	1	<0.1%
Impaired healing	1	<0.1%
Chest pain	1	<0.1%
Pyrexia	2	0.1%
Multi-organ failure	1	<0.1%
Edema peripheral	1	<0.1%
Inflammation	1	<0.1%
Asthenia	1	<0.1%

MO JUMP analysis ADAE3 SUR.

Selected SAE in this SOC are listed below.

301/ 606-020	33 M. MULTI-ORGAN FAILURE. After 15 doses of DAC 150. Onset Day 419. Drug withdrawn. Associated with Kawasaki syndrome, multiorgan failure and evidence of systemic vasculitis. He had fever, myalgia, joint pain, thrombocytopenia and proteinuria. Testing of MPO-ANCA was positive. Sepsis was suspected. The case was coded as bacterial, viral and fungal infection, and treated with multiple agents. No organism was identified. Event reported as resolved on Day 445. <i>(For detailed narrative see Infections SOC, although this could be also be immune mediated systemic inflammation)</i>
202/ 363-008	INFLUENZA LIKE ILLNESS. 26 M. DAC 150 in study 201/Placebo in 202; mild intensity Onset Day 447, End D468. Accompanying SAE of aseptic meningitis. <i>(See narrative under Infections SOC; this could also be immune-mediated)</i>
303/ 453-048	PYREXIA. 35 M. on DAC HYP 150, severe. Onset D713, End D737. Drug withdrawn because of suspected Brucellosis after 1 dose in 303 (27 doses total). <i>(See narrative under Infections; complex clinical picture)</i>
303/ 609-013	OEDEMA PERIPHERAL. 37 M. on DAC HYP 150, moderate. Onset D1162, End D1165. Also developed generalized eczema, lymphadenopathy and lung disease, suspected of DRESS. There is little information about the edema event <i>(see narrative under Skin disorders)</i>
303/ 611-015	INFLAMMATION . 36 M. DAC 150/DAC 150, had atypical MS with tumor like demyelination leading to drug withdrawal. Aspiration pneumonia, inflammation and septic shock occurred within 180 days after last dose of DAC HYP because of MS progression. <i>(See narrative under SAE in Nervous system disorders SOC.)</i>

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Reviewer comment: Three of the patients discussed above had systemic symptoms treated empirically as an infection but no organism was identified (301/606-020, 303/453-048, 303/609-013), suggesting the possibility of an immune mediated systemic inflammatory reaction.

I believe that because of the decrease in Tregs and NK cell expansion, and the time course of these events, DAC HYP may have played a role in all these cases. The case of aseptic meningitis could have been also immune-mediated. For additional discussion see section 8.5.3 of this review.

- **SAE Hepatobiliary disorders SOC and Liver Investigations**

Patients with SAE in the Hepatobiliary disorders SOC and/or the Investigations SOC/Hepatobiliary HLGT in the controlled studies are summarized in Table 19.

Table 19. SAE in the Hepatobiliary SOC and Investigations/Hepatobiliary HLGT in controlled studies 201 and 301.

	Study 201			Study 301	
	DAC150	DAC300	Placebo	DAC150	IFNβ1a
	N=207	N=208	N=204	N=919	N=922
SAE	3 (1.4)	1 (0.5)	1 (0.5)	8 (0.9)	7 (0.8)
DILI	2 (1.0)	1 (0.5)	0	5 (0.5)	1 (0.1)

All SAE listed in SOCs. DILI: cases consistent with drug induced liver injury upon review of narratives.

Does not include one case that in my opinion is consistent with mixed hepatocellular and cholestatic DILI but as per Dr. Avigan was a case of cholangitis,

Upon review of the narratives, excluding AEs of cholelithiasis and cholecystitis, there were three SAE consistent with Drug Induced Liver Injury (DILI) in study 201 (two in the DAC150 group (toxic allergic hepatitis and ALT elevation [17x ULN]) and one on DAC 300 (jaundice/liver necrosis)). There was none on placebo. In study 301, there were five SAE consistent with DILI in the DAC 150 group (including acute hepatic failure, DILI, acute hepatitis and two cases of hepatitis toxic) as compared to one hepatitis toxic in the IFNβ1a group. *(These numbers do not include the case of cholangitis).*

In my opinion the findings indicate that the liver safety profile of daclizumab is less favorable than that of IFNβ1a.

Patients with SAE in the Hepatobiliary and Investigations (Hepatobiliary) SOCs in the Total DAC experience are shown below.

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Table 20. SAE in Hepatobiliary and Investigations (Hepatobiliary) SOC, Total DAC HYP

	Total DAC N=2336	
	n	%
TOTAL	30	1.3
ANY IN HEPATOBILIARY SOC	23	1.0
ACUTE HEPATIC FAILURE	1	<0.1
AUTOIMMUNE HEPATITIS	3 ¹	0.1
CHOLECYSTITIS	2	0.1
CHOLECYSTITIS ACUTE	1	<0.1
CHOLECYSTITIS CHRONIC	1	<0.1
CHOLELITHIASIS	3	0.1
CHRONIC HEPATITIS ²	1	<0.1
DRUG-INDUCED LIVER INJURY	1	<0.1
HEPATIC STEATOSIS	1	<0.1
HEPATITIS	1	<0.1
HEPATITIS ACUTE	1	<0.1
HEPATITIS TOXIC ³	4	0.2
JAUNDICE	3	0.1
JAUNDICE HEPATOCELLULAR	1	<0.1
LIVER DISORDER	1	<0.1
ANY INVEST (HEPATOBIL HLGT)	8	0.4
ALT INCREASED	3	0.1
AST INCREASED	3	0.1
BLOOD BR INCREASED	1	<0.1
GGT INCREASED	1	<0.1

Source: Medical Officer analysis. ADAE3 datasets. SUR.

¹ Three cases reported as a autoimmune hepatitis (AIH) in datasets, one fatal. ² Acute exacerbation of chronic immune hepatitis ³ One of these cases of hepatitis toxic had a diagnosis of AIH as per a consultant hepatologist and two had the preferred term changed to AIH subsequent to the cutoff of the SUR. Therefore, there are at least 7 cases of AIH in the Total DAC.

At the time of the SUR, 30 patients had SAE in the Hepatobiliary disorders SOC or the Investigations SOC (Hepatobiliary HLGT). After review of each of the individual cases of acute hepatic failure, drug induced liver injury, hepatitis acute, hepatitis toxic, autoimmune hepatitis, jaundice, and jaundice hepatocellular it is clear that they many of these terms represent the same event: serious drug induced liver injury (total of 18 cases).

Selected narratives of SAE in Hepatobiliary disorders and Investigations (Hepatobiliary) SOC are included below. Additional listings and narratives of events in these SOC are presented in Appendix 13 of this review (13.3.4.)

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Selected narratives of SAE in Hepatobiliary disorders and Investigations (Hepatobiliary) SOCs

203/ 759-008	<p>JAUNDICE HEPATOCELLULAR and skin rash. 34 M. No relevant Hx or concomitant meds. Had toxic skin eruption (urticarial, on arms, hands and trunk), on Day 1383 leading to drug suspension treated with topical treatment. On Day 1422 ALT <2xULN. On Day 1425 thru 1427 had upper resp infection treated with paracetamol/ pheniramine/ phenylephrine. On Day 1432 presented severe elevated ALT (22X ULN)/AST (20X ULN)/BR (8X ULN). Events listed as ending on day 1440. However, on Day 1440 Dx of hepatocellular jaundice was made, reported as resolved on day 1462 along with the rash. Labs: Hyperglobulinemia (mostly serum IgE and IgG) without a spike. Liver US: diffuse steatosis, hepatomegaly and chronic cholecystitis. Drug withdrawn. No bx; no CS treatment. Daclizumab antibodies were negative throughout the study except on Day 1065 (DAC ab old assay 23.3), Day 1511 (DAC ab new assay 240)(at early termination visit). <i>Pt had DILI with mixed hepatocellular and cholestatic component. The patient used paracetamol only for 2-3 days approximately 1 week prior to the event of ALT elevation. Moreover, the event of hepatocellular jaundice was preceded/accompanied by an event of rash. In my opinion DAC may have played a role in this case.</i></p>
203/ 506-011	<p>AUTOIMMUNE HEPATITIS. 32 F. Diagnosed after 645 days in study 203. She received 26 doses of DAC 300 in 201 and 202 and 23 doses of DAC 150 in study 203 (45 doses). Throughout the study LFTs remained within normal except for 2 transient elevations to <1.4x ULN in Days 282 and 310 and 1.6xULN on Day 590 (day of last dose). One day after the last dose, she was hospitalized for MS relapse, treated with IV MP. On Day 648 local lab showed ALT of 231 U/L and AST of 129 U/L (normal not provided). Drug was withdrawn. On Day 654 she was hospitalized for further workup. On Day 677 (approximately 2 months after the last dose of DAC and of IV MP) ALT was 22xULN, AST 13xULN, BR <2xULN. Treated with oral prednisone. No biopsy. On Day 698, ALT <4xULN, AST 1.3xULN and normal BR. Liver enzymes completely normalized (b) (6). Patient continued on low dose prednisone until September 2013 and considered resolved. As per follow up IND safety reports (submitted in October and November, 2015) the event of AIH is ongoing, with Normal LFTs but the subject continues to take prednisone 5 mg daily and started azathioprine 75 mg daily in September 2014. <i>AIH diagnosed after 45 doses of DAC. The patient developed AIH two months after last dose of DAC and IV MP. Still requires corticosteroid and azathioprine 2 and ½ years after last dose of DAC.</i></p>
303/ 667-017*	<p>IND Safety report submitted Jan 15, 2016. 49 F. Hospitalized for drug induced liver injury and generalized eczema (b) (6), 17 months into study 303 (unknown number of doses). Last dose of drug was (b) (6) (stopped because of ALT elevation). By 10/8/15 ALT was 9xULN (normal BR). Liver ultrasound and hepatitis serology negative. ANA + 1:40. Liver autoABs negative. On (b) (6) diagnosed with toxic hepatitis. No biopsy. ALT normalized (b) (6) eczema resolved. On (b) (6), she was readmitted with fever, vomiting, diarrhea, hyperglycemia and dehydration and was diagnosed with toxic pancreatitis (amylase 1240 [normal up to 400], “voluminous pancreas” on imaging) and Type I diabetes mellitus. Glucose was 17.6 mmol/L (normal 4.1-5.9). Elevated IGE and eosinophilia. All events were considered related to DAC. Treatment included hydration</p>

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	<p>and insulin. The patient was discharged (b) (6) with normal amylase. <i>This patient had a cluster of immune mediated conditions: DILI, exanthematous maculopapular rash, pancreatitis and Type I diabetes mellitus, within 6 months of the last dose of DAC. He also had eosinophilia. The event of Type I DM is ongoing. It is unclear if patient was treated with corticosteroids. Follow up is expected. This case is consistent with an IPEX-like syndrome or DRESS.</i></p>
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Of the 18 SAE consistent with DILI as of the SUR, two occurred with DAC300 (202/909-001 and 202/765-003) and 16 occurred with DAC150 (one had previously received DAC300). The time to onset of these events ranged from 57 days to more than 3 years of exposure to DAC, and included some that started up to 2 months after the last dose of DAC. In term of number of doses, the patients had received 3 to 60 doses of DAC. Clinical manifestation ranged from asymptomatic liver enzyme elevation to liver failure. Drug was discontinued in all cases even though the datasets may say that “no action was taken with drug.”

At least seven of these 18 patients underwent a liver biopsy, which was consistent with DILI or autoimmune hepatitis (AIH). Some had concomitant immune mediated adverse reactions, such as cutaneous reactions and thrombocytopenia. Some were confounded by hepatotoxic medications (paracetamol, IV MP, carbamazepine, valproate, escitalopram) or possible viral infections. Half of the 18 cases were thought to be related to DAC by the investigators. I believe that DAC may have played some role in most of these cases. *(For additional assessment of these cases see two consultative reviews by FDA hepatologists Dr. Mark Avigan and Dr. John Senior.)* All but one of these 18 cases (202 909-001, fatal autoimmune hepatitis) were reported to have resolved one to several months after DAC discontinuation. However, at least 8 of the 16 cases were treated with high dose corticosteroids and/or immunosuppressors and some the cases reported as resolved are still on low dose corticosteroids and azathioprine (one of them >2.5 years after stopping DAC), therefore, they were not resolved.

In addition to the cases discussed above, at least 3 more cases consistent with DILI were reported after the cutoff of the SUR (302/512-103* and 303/543-010*, included in Appendix 13.3), and 303/667-017* (who also developed eczema and Type I DM, described in the previous page).

In addition to the SAE reported in the Hepatobiliary and Investigations SOC, one case of ALT >47xULN consistent with DILI was reported as a non-serious AE in the Congenital SOC (201/509-007, arteriovenous malformation; ALT elevation resolved after DAC discontinuation). ALT values were not captured as an AE in the Investigations SOC. In my opinion an increases in ALT of 47xULN should have been reported as a SAE (an important medical event). In addition to these cases, two events coded as bacterial infections [hepatocystitis and hepatic brucellosis] had no serology or lab information to support the diagnoses and are consistent with DILI (or a systemic immune process involving the liver). Also one case with ALT >30x ULN

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was coded under the GI disorders SOC as “celiac disease causing elevated liver enzymes.” I agree this was celiac disease, but I believe that it may have been induced by DAC HYP.

Reviewer Comment: There are at least 21 SAE consistent with DILI in this application. Of all cases of potential DILI, at least 7 cases were AIH. This observation raises serious concerns regarding DAC HYP’s safety profile. For further discussion of DILI with DAC HYP see Section 8.5.1 of this review.

- **SAE in Investigations SOC other than liver related**

The only SAE in this SOC that were not liver related were one case of abnormal cervix smear (301/413-002) and one of amylase increased. This patient (301 453-033, 55 F) had elevated ALT from the beginning of the study; developed increased amylase on Day 621, a few days after treatment with IV MP without ALT/BR increase. Event resolved after one day.

An additional SAE of amylase increased and pancreatitis was reported in a patient who also had DILI, eczema and Type 1 DM (303/667-017*), which appears related to DAC (included above, under Hepatobiliary SAE).

- **SAE in the Immune Disorders SOC**

Acute hypersensitivity reactions

Two SAE of hypersensitivity occurred in the controlled studies (one with DAC 300 in study 201, one on DAC 150 in study 301) and one anaphylactic reaction occurred with IFNβ1a in study 301. Two additional cases of “drug hypersensitivity” were reported in the extension studies as of the SUR, and two 15-day reports were submitted in this SOC after the cutoff of the SUR (one of acute urticaria and one of anaphylaxis). Selected patients with SAE in Immune system disorders SOC in Total DAC HYP database are summarized below. *In my opinion the cases below are related to DAC.*

303/ 557-005 *	(2015BI038894) 25F. No concomitant meds. No Hx of allergy. Received 37 doses of DAC HYP 150 as of study 303. On March 18, 2015 she presented an “allergic reaction” and was seen in outpatient clinic (unclear how long after the dose). Treatment included IV prednisolone, IV fluids and electrolytes. She was hospitalized with acute urticaria (b) (6). Treatment included IV saline and calcium gluconate IV. Esophago gastroduodenoscopy and fluorography of lungs were performed for unclear reasons. At the end (b) (6) a dermatologist diagnosed acute urticaria . Medication included topical prednisolone and dexamethasone. DAC HYP was discontinued. As of June 2015 the event was still ongoing. A skin biopsy was consistent with spongiotic (seborrheic/eczematous) dermatitis. <i>This case is consistent with urticaria and eczematous dermatitis after 37 doses of</i>
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	<i>DAC. The fact that fluorography of lungs and EGDuodenoscopy were done suggest that there may have been some respiratory distress or airway compromise. However results are not available</i>
203/ 555-001 *	(2015BI134574). 42 F, presented “ anaphylaxis ” and “toxic skin eruption” on (b) (6) after 68 doses of DAC HYP. In (b) (6) she presented fever and weakness, initially treated as pneumonia, without response to antibiotic treatment. Chest CT showed hilar adenopathy. In (b) (6) a bronchoscopy and biopsy showed sarcoidosis . Event eventually resolved, apparently without corticosteroids. In (b) (6) a rash appeared on both thighs and then the whole body. Three days later she had tongue swelling , hoarse voice and almost fainted. She was treated with chloropyramine and methylprednisolone, calcium and potassium and discharged 24 hours later. DAC HYP was discontinued. Patient is currently on oral methylprednisolone. <i>Anaphylaxis after 68 doses of DAC</i>

Additionally, four patients (301/658-006, 202/765-012, 202/353-003 and 203/453-015) had hypersensitivity to specific agents (methylprednisolone, arthycain, wasp sting and penicillin respectively) and are reported to have continued DAC HYP treatment without further allergic reaction. Therefore, they are unlikely related to DAC HYP.

301/441-021, a 40 yo F had non-SAE of angioedema after 8 doses of DAC150, associated with cough, fever and slight dyspnea. She thought she had probably been stung by an insect. She was treated with betamethasone and prednisolone among other treatments. Subsequently she developed a SAE of angioedema the day after the 9th dose of DAC150 causing hospitalization. On examination she had fleeting and migrating erythematopapulous plaques on the trunk, thighs, and face, and stabbing chest pains. Routine lab testing was normal. Serology was negative for hepatitis C, B, HIV, CMV and Mycoplasma, and positive (old immunity) for EBV and Parvovirus. Event was attributed to a “possible viral etiology”. The event resolved 2 months after its onset. The patient continued to receive DAC150 (25 total doses).
It is hard to attribute to DAC150 if the patient continued treatment without further events, although it is unclear how long she continued taking prednisone after the event.

Additionally, 201/752-010 a 36 year old male Presented an AE of hypersensitivity, syncope and circulatory collapse after the first dose of DAC 300. He was treated with IV prednisolone and IV fluids. BP before dose was 125/80; ECG was normal; 4 hours after dose BP was 105/70, pulse 75 bpm. ECG not reported. Drug was withdrawn. Anti DAC and neutralizing antibodies were negative. Normal eosinophils. IgE levels not provided. *There is little description in the narrative. The investigator at the site thought it was an allergic reaction and treated the patient with corticosteroids but it is unclear whether this was in fact a hypersensitivity reaction.*

At least one SAE of acute urticaria and one of anaphylaxis that appear related to DAC HYP occurred after 2 to 5 years of treatment. For additional discussion of hypersensitivity see Section 8.5.3 of this review.

Other immune reactions

SAE consistent with immune mediated reactions were reported under SOC's other than the Immune system disorders, such as the Musculoskeletal disorders SOC (e.g. rheumatoid arthritis (RA) and the GI disorders SOC's (e.g. ulcerative colitis). Moreover, there are several cases consistent a systemic inflammatory condition suspected of sepsis with no organism (mentioned under General disorders SOC's and Infections). Both the applicant and this reviewer conducted analyses of autoimmune diseases potentially related to DAC HYP.

On May 13, 2015, in response to the FDA 74-day filing letter, the applicant submitted analyses of allergic and immune mediated events in the controlled studies and the Total DAC database, including PTs that had not been included in the original application. Specifically, DNP asked that events of inflammatory colitis (e.g. ulcerative colitis) be included in the analyses of potential autoimmune disorders. The list of PTs appeared adequate in general. However, the search was based on the reported PT, not on the final diagnoses (e.g. only 3 cases of AIH), it was missing terms such as sarcoidosis and alveolitis, and included terms that did not belong to the autoimmune category (e.g. seasonal allergy, ischemic colitis). Of note, there was at least one SAE of pulmonary sarcoidosis in the original BLA application (303/611-029), but it was coded under the Respiratory and Thoracic disorders SOC. Additional cases of sarcoidosis were submitted after the cutoff of the SUR, including one case of biopsy proven renal sarcoidosis that was not submitted to FDA as an IND safety report because the investigator thought it was related to DAC HYP (303/325-001).

With these caveats, the applicant's exploratory analyses showed that the serious potential allergic and autoimmune disorders was greater in DAC treatment groups as compared to placebo (1% for DAC150, 2% for DAC300 and none on placebo in study 201) and compared to IFNβ1a (1% for DAC HYP 150 mg vs. 0.1% on IFNβ1a in study 301). In these analyses, the rate for the Total DAC HYP experience was 2% (cut-off February 2014).¹⁴ (Data not shown.)

As part of the SUR, the applicant submitted an analysis of autoimmune diseases. As of November 2014, the applicant identified only 10 patients with serious autoimmune diseases in the Total DAC HYP experience (0.5%). This list included autoimmune hepatitis, autoimmune thyroiditis, Basedow's disease, celiac disease, lupus-like syndrome, myasthenia gravis, pernicious anemia and Reiter's syndrome. Again, inflammatory gastrointestinal disorders were not included in the analyses. Neither were the cases of psoriasis or eczema.

¹⁴ In the applicant analyses, the rate of Immune mediated events in study 201 was 5%, 7% and 4% for DAC150, DAC300 and placebo, respectively. The rate of events in study 301 was 15% and 9% on DAC150 and IFNβ1a, respectively. The rate in the Total DAC database as of the original submission was 16% (data not shown).

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While these analyses show an increased risk of immune-related SAE with DAC HYP as compared to placebo and IFNβ1a, they failed to capture several events and underestimate the risk of autoimmune diseases associated with DAC HYP. It is unclear why the applicant does not pool the events of colitis and psoriasis with the other autoimmune processes. Additionally, the analyses do not include events that occurred after the cut-off of the SUR (e.g. immune hemolytic anemia, sarcoidosis). I conducted my own analyses of potential autoimmune disorders in study 301 and the Total DAC HYP database. For further discussion see Section 8.5.3 of this review.

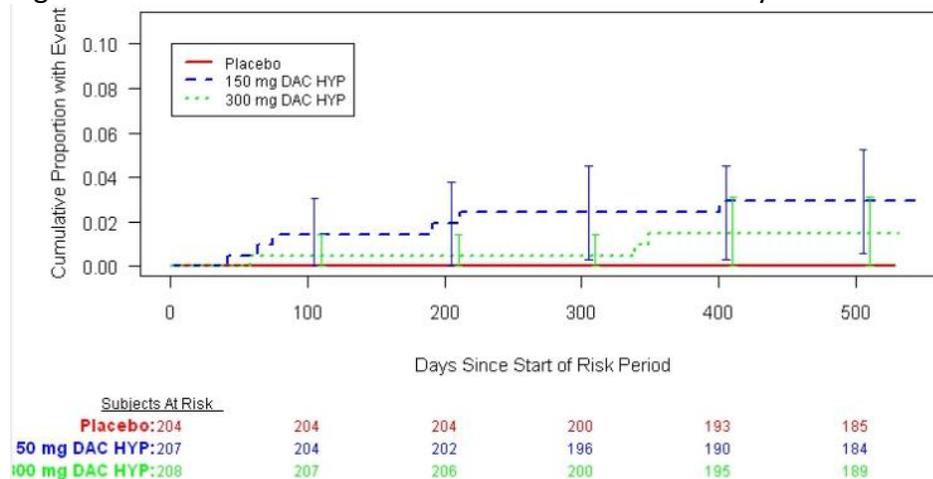
- **Patients with SAE in Infections and Infestations SOC**

SAEs in this SOC occurred more frequently for DAC HYP 150 (6 of 207 (2.9%) subjects (including one Hepatitis B and one CMV reactivation) and for DAC HYP 300 (3 of 208, 1.5%, including one case of yersinia infection) compared to none in placebo in Study 201.

SAEs in this SOC occurred more frequently for DAC150 (40 of 919, 4.4%) compared to IFNβ1a (15 of 922, 1.6%) in Study 301. Preferred terms that occurred in at least 2 (0.4%) of patients are listed as follows (all were more frequent on DAC150 as compared to IFNβ1a): urinary tract infection (8 vs. 2, respectively), pneumonia (6 vs. 2, respectively), appendicitis (3 vs. 0, respectively), cellulitis (2 vs. 0 respectively) and pyelonephritis (2 vs. 1, respectively). One case of tuberculosis was reported in the DAC150 group, and none on IFNβ1a.

Summary tables for analyses of **infections SAE** in studies 201 and 301 are presented in Appendix 13 of this review (13.3.3). Time to event analyses in these trials is shown below.

Figure 1. Cumulative rate of SAE of infections SOC in study 201



Empirica Study analysis run 6/23/15

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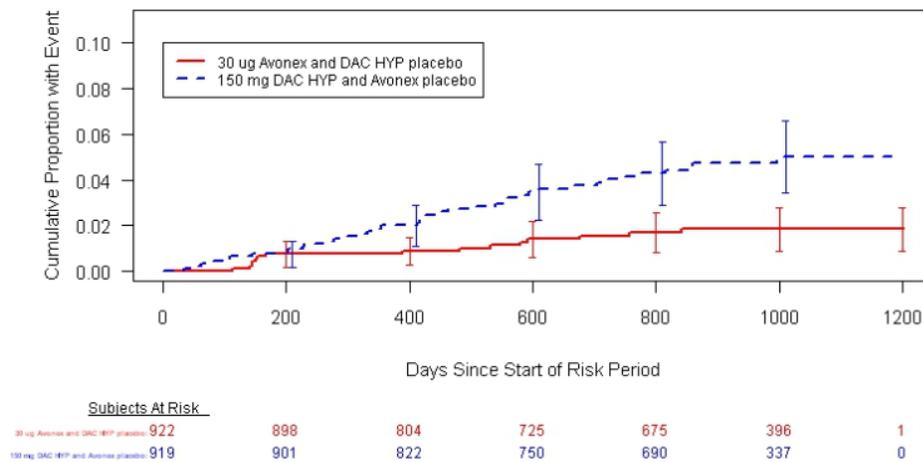
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When looking at SAE of infections the rate is higher in patients on DAC150 than DAC300. I believe the trial is too small to allow conclusions regarding a dose response between DAC150 and 300 mg.

Figure2: Cumulative rate of SAE of Infections SOC in study 301



Empirica Study analysis run 6/23/15

In study 301, the risk of SAE of infections with DAC HYP increases after Day 200 and becomes statistically significant different from IFNβ1a after Day 600.

A summary table of all infections in the Total DAC database as of the SUR, by SOC, HLGT and HLT is shown below (as per this MO analysis using JUMP).

Table 21. Patients with SAE in Infections SOC by HLGT, HLT and PT

HLGT HLT PT	DAC HYP N=2236 (5214 PYRs)	
	n	%
UNIQUE PATIENTS WITH SAE IN THIS SOC	99	4.4%
INFECTIONS - PATHOGEN UNSPECIFIED		
LOWER RESPIRATORY TRACT AND LUNG INFECTIONS Pneumonia (n=15), lobar pneumonia (n=1), lung infection (n=2), atypical pneumonia (n=1), bronchitis (n=5)	24	1.1
URINARY TRACT INFECTIONS Urinary tract infection (n=15), Pyelonephritis (acute, chronic or NOS, n= 3), genitourinary tract inf (n=1), cystitis (n=1)	20	0.9

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UPPER RESPIRATORY TRACT INFECTIONS Sinusitis (n=3), Tonsilitis (n=2), Upper respir. Inf (n=2) Acute sinusitis, chronic tonsilitis, peritonsillar abscess, pharyngitis, rhinitis, tracheobronchitis (n= 1 each)	12	0.5
ABDOMINAL AND GASTROINTESTINAL INFECTIONS Appendicitis (n=5, incl. 1 perforated), gastroenteritis, gastrointestinal infection, enteritis infectious, enterocolitis, diverticulitis (one each)	10	0.4
INFECTIONS NEC Respiratory tract infection (n=2), wound infection, device related infection, pelvic abscess, localized infection, infection (one each)	7	0.3
DENTAL AND ORAL SOFT TISSUE INFECTIONS Parotitis (n=2), Ludwig angina (n=1)	3	0.1
SEPSIS, BACTERAEMIA, VIRAEEMIA AND FUNGAEMIA NEC Urosepsis, septic shock, sepsis (one each)	3	0.1
CENTRAL NERVOUS SYSTEM AND SPINAL INFECTIONS Aseptic meningitis	1	<0.1
EAR INFECTIONS Ear infection	1	<0.1
MUSCLE AND SOFT TISSUE INFECTIONS Psoas abscess	1	<0.1
SKIN STRUCTURES AND SOFT TISSUE INFECTIONS Furuncle	1	<0.1
BACTERIAL INFECTIOUS DISORDERS		
BACTERIAL INFECTIONS NEC Cellulitis (n=3), bacterial infection, upper resp infec bacter.	5	0.2
CLOSTRIDIA INFECTION C. Difficile colitis	2	0.1
BORRELIAL INFECTIONS Lyme disease, neuroborreliosis	2	0.1
OTHER HLTs (one event each) Brucellosis, klebsiella infection, salmonellosis, Streptococcal urinary tract infect, Yersinia infection	5	0.2
VIRAL INFECTIOUS DISORDERS		
Viral infection (n=3), infectious mononucleosis (n=2), chronic hepatitis B, CMV infection, dengue fever, Hepatitis A, Hepatitis C, herpes zoster, influenza, meningitis viral, varicella (one each)	13	0.6
MYCOBACTERIAL INFECTIOUS DISORDERS		
Mycobacterium abscessus infect, pulmonary TB (one each)	2	0.1

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ANCILLARY INFECTIOUS TOPICS		
Reiter's syndrome (n=1)	1	<0.1
CHLAMYDIAL INFECTIOUS DISORDERS		
Chlamydial infection (n=1)	1	<0.1
FUNGAL INFECTIOUS DISORDERS		
Fungal infection (n=1)	1	,0.1

Source: ADAE 3, SUR. MO JUMP analysis. Table generated manually based on HLGT/HLT analysis.
 One patient may have more than one event.

Most common serious infections with DAC HYP were respiratory tract infections (at least 36 patients (1.6%) had a SAE of either a lower or upper respiratory tract infection), followed by urinary tract infections. In general, the risk of infections increased with time.

The exact number of opportunistic infections and whether they are related to treatment with DAC is difficult to determine in this database because the available information does not always allow distinction whether an infection is new or a reactivation of a previous infection (e.g. EBV, hepatitis C infections). Moreover, the final diagnoses are not provided in some patients (e.g. one case of "pneumonia, probably TB"). Additionally, some of the events reported as infections may potentially have been immune mediated events (e.g. Kawasaki's syndrome; some cases of interstitial lung disease/pneumonitis, one case of aseptic meningitis and two cases of c difficile colitis).

I acknowledge the complexity of some of these cases and how difficult is for the investigators to assess and treat these patients, however, if a final diagnosis is not established in the clinical trial setting it is unlikely to be reached in the postmarketing setting, and patients will be subjected to extensive workups and perhaps unnecessary antibiotic/antiviral/antifungal treatments.

SAE of infections will be briefly discussed in the following order: Most common infections (respiratory, urinary, sepsis/suspected sepsis); mycobacterial infections; specific bacterial infections; sepsis/suspected sepsis; viral infections. Additional listings and narratives are presented in Appendix 13 of this review (Appendix 0 Listings and narratives of Infections).

Serious Respiratory infections

Twenty four patients had SAE of pneumonia/lung infection with unspecified organisms. They were 17 female, 7 male, mean age 40 years, range 22 to 53 years (median 41). Time to onset was 559 days (± 396), median 479 days, range 45 to 1201, with a cumulative rate of 1% by the cut-off date of analysis. The duration of the SAE of pneumonia among those who have starting and end date was mean 26 days; median 15 days, range 3 to 111 days. These estimates do not include 3 SAE of aspiration pneumonia and sepsis (aspiration pneumonia is coded under the Respiratory, thoracic and mediastinal disorders SOCs). There is an imbalance in the numbers of cases of pneumonia between DAC and IFN β 1a in study 301. Daclizumab increases the risk of serious pneumonia.

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The datasets do not include information as to why these were determined to be Serious AEs but most of them are likely to have been hospitalized. As per the listings, only 4 of these cases of pneumonia led to drug withdrawal, 4 lead to drug interruption, and three did **not resolve**. Three cases of pneumonia (303/552-014, 303/301-010 and 303/ 611-049) were consistent with atypical pneumonia or immune mediated pneumonitis (because of the protracted course, lack of response to antibiotic treatment, ground glass/nodular lung changes and mediastinal lymphadenopathy). These cases are consistent with an immune mediated process.

Urinary infections

The next most common infections after respiratory infections were urinary tract infections. Nineteen patients presented serious urinary infections, including urinary tract infection, pyelonephritis (acute, chronic, no otherwise specified) or urosepsis in total DAC HYP at time of the SUR (0.8%). Some patients presented more than one event (once in the base study and another one in one of the extension studies). A listing of SAE UTIs is included in Appendix 13 of this review (13.3.10).

Of the 19 patients with SAE of urinary infections, 13 were female and 6 were male, mean age was 43 years. Time to onset to the first urinary infection was 375 days (range 63- 1658) and the mean duration, -for those with an end date- was 15 days (range 2 to 109 days). The majority of the cases did not provide a specific pathogen. There was one case of UTI by streptococcus pneumonia. Only two of the cases are listed as leading to drug withdrawal (203/109-003 and 301/254-012), and one was not resolved (303/311-004).

Pneumonia and urinary tract infections are not uncommon in patients with MS. However, the rate of such infections was greater with DAC150 than IFNβ1a in study 301. There were also a higher number of cases of SAE of appendicitis on DAC HYP in study 301 (3 vs. 0).

Mycobacterial infections

There were two SAE of mycobacterial infections as of the ISS (one m. tuberculosis [301/611-009] and one m. abscessus [202/303-006]) after 13 and 11 doses of DAC HYP, respectively. They were reported as resolved. The case of m. abscessus may have been a contaminant –an incidental finding in a patient with bacterial pneumonia; this patient also underwent bronchoscopy and did not receive anti TB treatment.

Patient 301/611-009. 34 M from Poland had AE of pulmonary TB after one year of DAC HYP treatment. He had fever and multiple pulmonary nodules of unknown origin. Diagnosis was made after an open biopsy of a right lung nodule that showed granulomas with necrosis. Risk factors included exposure as a healthcare worker. Drug was discontinued. It is unclear if this is primary TB or reactivation, because apparently he did not have apical disease. There is no information about duration of treatment.

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303/747-005* was reported as “probable TB” after the cutoff of the SUR. The case occurred after 48 doses of DAC HYP and was associated with anemia, hyponatremia, hypokalemia, hypoproteinemia. The patient had a bronchoscopy and transbronchial lung biopsy that showed granulomatous inflammation. Workup included a bone marrow biopsy. Differential diagnosis still includes aspergillus infection. She is being treated empirically with anti TB drugs and antifungals, after protracted hospitalization. The narrative for this patient is presented in Appendix 13.3.11 of this review. *Follow up for this patient is pending as of January 2016. If no evidence of infection is found, I think it could be consistent with sarcoidosis.*

In addition to the 2 cases of TB, 3 non-SAE of TB were also reported with DAC HYP. I would think that TB should be considered always a SAE.

Additionally a 50 F from Russia in study 303, had a SAE of pneumonia after 5 doses of DAC HYP. The Investigator later changed the event term to “Tuberculosis of left lung.” Subsequent to database lock for this submission, the investigator changed again to “community acquired polysegmental pneumonia.” It is unclear if the patient received any treatment for TB.

Serious Bacterial infections with specific agents

Most reports of infections did not identify a specific pathogen, however, some specific bacteria were reported in this database, and included hepatic yersiniosis (201/752-018); brucellosis (303/453-048); neuroborreliosis (301/600-018); clostridium difficile colitis (202/501-013 and 303/622-016) and Lyme disease (301/600-018 and 301/610-009). These serious infections occurred after 11 to 56 doses of DAC HYP.

There is no adequate data to support the diagnoses of yersiniosis or brucellosis. I believe the case of yersiniosis is consistent with drug induced liver injury, or perhaps a case of early DRESS, because there is not enough data to rule out involvement of other organs. DAC HYP treatment was stopped after 11 doses because of a drug eruption. Two months after the last dose, the patient presented ALT elevation >30xULN with BR<2xULN. The investigator initially reported the case as Hepatitis B, but then changed to yersiniosis with no adequate evidence for either. Extended narrative for this patient is in Appendix 13.3.11.

The case diagnosed as brucellosis was initially reported as “Pyrexia”. The clinical picture is reminiscent of a systemic immune reaction such as DRESS. There is no mention of eosinophilia but the diagnosis of DRESS does not require eosinophilia. See summary below and extended narrative in Appendix 13.3.11.

Patient 303/453-048 had a very complex clinical picture. He developed pneumonia after 25 doses of DAC150 (first and last dose in study 303, study Day 692) that resolved after treatment with clarithromycin and levofloxacin, but he was re-hospitalized because of persistent fever,

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arthralgia, hepatosplenomegaly, ALT elevation, pulmonary consolidation, pancytopenia and +ANA (1:80). A diagnosis of brucellosis was made on Day 713 of DAC exposure. A lymph node biopsy was suspicious of lymphoma but the bone marrow biopsy was not definitive for lymphoma and the patient improved after treatment with rifampin and minocycline. He was also treated with prednisone 5 mg day (for “erythema”). He was discharged 3 weeks later with diagnosis of **brucellosis with secondary hepatitis**. It is unclear how long this patient took to fully recover after DAC HYP discontinuation. *By the way, several events were not captured in the AE datasets. This is all that the datasets show about this patient (no pancytopenia, no lymphadenopathy or suspected lymphoma, no bone marrow biopsy).*

USUBJID	PT	Ser	Action with DAC	Onset rel day	End rel day	Outcome
303/453-048	INJECTION SITE PAIN	N	NONE	171		NOT RESOLVED
303/453-048	MIGRAINE	N	NONE	171		NOT RESOLVED
303/453-048	PNEUMONIA	Y	NONE	692	718	
303/453-048	PYREXIA	N	NONE	692	708	
303/453-048	BRUCELOSIS	Y	DRUG WITHDRAWN	713	759	
303/453-048	PYREXIA	Y	DOSE INTERRUPTED	713	737	
303/453-048	BENIGN NEOPLASM OF THYROID	N	NONE	714		NOT RESOLVED
303/453-048	HYPERTRANSAMINASAEMIA	N	NONE	714	759	
303/453-048	DEPRESSION	N	NONE	737		NOT RESOLVED
303/453-048	ERYTHEMA	N	NONE	752	762	

As per additional information submitted on July 30, 2015 in response to an FDA request, the diagnosis of brucellosis was based on a reportedly positive IgM serology for Brucella. “The subject is from Catania, Italy, where brucellosis is endemic.” “The patient improved with Brucella treatment.” In my opinion there is insufficient information to accept the diagnosis of brucellosis. Brucellosis is a zoonotic infection transmitted to humans by contact with fluids from infected animals (e.g. sheep) or derived unpasteurized products (e.g. cheese). The best diagnostic test is bone marrow culture. It is among the typical causes of “fever of unknown origin” in any medical textbook, but it is rare. This occurred in a patient receiving a drug that may increase the risk of immune-related diseases. The applicant reported that “IgM serology” for brucella was positive and that the patient improved with antibiotics. However, there is no mention of a positive bone marrow culture, although a bone marrow biopsy was done during workup for lymphoma. Serology may be difficult to interpret in areas where infection is endemic. No details are given about the methodology of the serologic testing or actual IgM titers for this patient. I believe this may be a case of DRESS. For further discussion see section 13.3.10 of this review.

There is no data to support the diagnosis of C. difficile either (which occurred after 30 and 34 doses of DAC HYP respectively). Rather they appear to be non-infectious, inflammatory colitis. Listing and narratives are presented in Appendix O of this review.

Sepsis, septic shock, suspected sepsis

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Three cases of sepsis/septic shock following aspiration pneumonia and one urosepsis were reported as of the SUR within the 180 day follow up. Two were fatal and described earlier under Deaths in patients with worsening MS. The third case of aspiration pneumonia and sepsis was a 36 year old male hospitalized after 43 doses of DAC, also in a patient with worsening MS (303/611-015). This patient had tumor-like demyelination with epilepsy and worsening EDSS before the event of pneumonia. *The event resolved after ICU hospitalization which included tracheostomy but the current status of the patient is unknown. The case is described under the Neurologic system disorders SOC.*

The case of urosepsis (303/610-010) was in a 48 year old female, on Days 184 to 201 of DAC HYP (not included among the 19 patients with SAE of urinary tract infection mentioned above). *The case resolved. It is unclear how long it took or if it resolved with sequela. As per an IND safety report of a case of sepsis of unknown origin (2015BI132251), there are a total of three cases of urosepsis in the DAC HYP database.*

Therefore, overall, there were 3 cases of aspiration pneumonia and sepsis and 3 of urosepsis in this database. Aspiration pneumonia and urosepsis are not uncommon in patients with advanced MS, although DAC HYP may increase the risk of a serious outcome.

Patients with **multiorgan failure suspected of sepsis of unknown source or organism** included 301/606-020 (Kawasaki syndrome) and 203/303-005 (hemophagocytic syndrome [HPS]). These cases are described in detail in Appendix 0 of this review. One additional case of sepsis of unknown origin with multiorgan failure was submitted as an IND safety report on January 15, 2016, as follows.

Patient 303/552-001* (IND report 2015BI132251) was a 51 year old female hospitalized for 3 weeks with fever and life-threatening multiorgan failure thought to have sepsis followed by MS relapse (b) (6) after 48 doses of DAC. The investigator assessed the events to be related to the study drug. DAC was discontinued and patient was treated with prednisolone (unknown dose). Prednisolone treatment was ongoing as of January 8 2016. As per follow up report from Jan 11, 2016, on (b) (6) she had herpes labialis followed by fever and allergic reaction of unknown etiology with toxic damage to the liver; skin rash with pruritus, diffuse interstitial changes in the lungs and subsegmental atelectasis on the left, with fluid in the pleural cavities. US showed diffuse changes in pancreas and splenomegaly. Labs showed HTC 29% (normal 36-42), ALT 214 (normal not provided but usually <50 therefore this is at least 4xULN); BR 2xULN, K 2.9, sodium 186. There was marked central lower paresis more prominent on the right side. CT of brain showed moderate “mixed hydrocephalus” (*unclear if new or old*). CSF analysis showed increased total protein (0.46 g/L – normal up to 0.33 g/L); no organism (*viral cultures and PCR not mentioned*). The patient improved and was discharged (b) (6) recovered with sequela of decreased EDSS (5.5) and limited walking. Discharge diagnosis was septicemia without diagnosed focus and multiorgan failure and secondary immune deficiency with underlying therapy with monoclonal antibodies. This report mentions

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one dose of prednisolone 60 mg IV followed by intramuscular methylethylpyridinol for MS relapse and acyclovir, both ongoing. The event was eventually reported as resolved with sequelae.

The patient was treated with high dose IV and intramuscular corticosteroids and was apparently discharged on oral corticosteroids. The clinical picture is consistent with multiorgan hypersensitivity or DRESS. There is no mention of eosinophilia, but the diagnosis of DRESS does not require eosinophilia. The applicant should clarify for how long the patient continued corticosteroid treatment.

A case of Adult onset Still's disease was reported after the cut-off date of the SUR but it is also consistent with a systemic inflammatory response, as follows.

303/645-015*. (15-day report 2015BI155468) 43 F diagnosed with Adult onset Still's disease after 21 doses of DAC150 (13 in study 301, 8 in study 303). She had developed fever and polyarthritis 3 months earlier. Last dose of DAC was in (b) (6). First symptoms of myalgia and arthralgia started (b) (6). On (b) (6) she was hospitalized with spikes of high fever, generalized toxic inflammatory rash and leg edema. At the time she had anemia (Hb 88) increased WBC (20,000), low albumin, ALT >2xULN, mild hepato splenomegaly and very high ferritin levels. A source of infection was not found despite extensive workup. A pulmonologist suggested that this systemic inflammatory response could be an allergic reaction to the study drug and recommended corticosteroid treatment. Her symptoms improved after treatment with oral methylprednisolone and intravenous dexamethasone. She was discharged from the hospital in good condition (b) (6) with a diagnosis of Still's disease adult onset (a systemic presentation of rheumatoid arthritis, which is rare in adults). The investigator did not think Still's disease was related to DAC. *I do believe that this systemic inflammatory response is related to DAC, whether it is RA or not. As per a response submitted by Biogen Idec on 3/3/16 subsequent to the late cycle meeting comments, these events resolved and DAC HYP was re-started without apparent problems. However, longer follow up is required before concluding that this case was unrelated to DAC HYP.*

*Because of the effects of DAC HYP on the immune system, I believe it may have played a role in the cases of sepsis/multiorgan failure described above (Kawasaki, HPS, sepsis of unknown origin) and the case of Still's disease adult onset. Moreover, I think that these cases with fever and multiorgan involvement may be a manifestation of a **multiorgan hypersensitivity syndrome/DRESS**. Whether these life-threatening cases of multiorgan failure were infectious or immune mediated, patients required extended hospitalizations, prolonged antibiotic treatment and invasive testing that likely affected the patients' quality of life. For additional discussion see Section 8.5.3 Immune mediated reactions.*

Appendicitis

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Five patients had SAE of appendicitis in the Total DAC HYP database. The cases are summarized below.

201/ 454-017	44 F. Had appendicitis and appendectomy after 3 doses of DAC HYP. Lymphadenopathy after 9 doses; hepatic enzyme increased (ALT 6x ULN) after 13 doses. Entered 202 and drug with withdrawn because of liver enzyme increased on Day 1 of treatment with placebo. ALT normalized 5 months after last dose of DAC. Exanthema was diagnosed on day 51 of study 202 and lasted about 1 month.
301/ 311-005	30 M. Had AE of thyroxine decreased after 6 doses, mild rash after 8 doses that resolved after 1 month; appendicitis and appendectomy, after 16 doses. Resolved and continued Rx.
301/ 659-006	26 F. MS relapse after 8 doses, bronchitis after 13 doses, appendicitis and appendectomy after 22 doses, resolved and continued treatment. Eczema after 24 doses lasted 1 1/2 months.
301/ 159-003	45 M. Presented myalgia after 1 dose of DAC150, abdom pain and constipation after 2 doses, musculoskeletal chest pain after 3 doses, appendicitis perforated with pelvic abscess requiring surgery. Also had drug hypersensitivity, ALT, AST, GGT increased, rash, oral herpes and skin exfoliation around the time of surgery, all resolved. DAC HYP was interrupted but continued. Patient also had depression after 7 doses and MS relapse after 23 doses (from Day 622 to 813). Treated with prednisone PO Day 672-674 for “non-protocol defined MS relapse”
202/ 553-004	23 F. Had an upper respiratory infection on Day 9-16, appendicitis on Day 65 requiring appendectomy after 3 doses of DAC150; lymphadenopathy onset on Day 230 after 10 doses and ALT 6xULN on Day 366 after 13 doses that led to withdrawal (both not resolved).

All 5 patients with appendicitis, including the case of perforated appendicitis with pelvic abscess continued DAC HYP treatment and completed the study. Four presented rashes lasting for 1-2 months that resolved despite treatment continuation. The patient who had the pelvic abscess reported transient liver enzyme elevation that resolved while on DAC. Therefore these events are not clearly related to DAC HYP. However, three of the cases of appendicitis were in study 301, versus 0 on IFN β 1a. Moreover, 201/454-017 developed rash, lymphadenopathy and ALT elevation 5xULN and 202/553-004 developed lymphadenopathy and ALT 6xULN a few months after the event of appendicitis, raising the possibility that appendicitis could be part of a DAC HYP related effect.

SAE of viral infections

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There was an excess of serious viral infections in studies 201 and 301 as compared to placebo and IFNβ1a, respectively. In study 201 there were 3 cases (one viral infection, one CMV hepatitis and one chronic hepatitis B, on in DAC HYP 150 mg) as compared to none on placebo. In study 301 there were 7 on DAC HYP 150 and 3 on IFNβ1a1a. The cases on DAC150 were one chicken pox (varicella), one Hepatitis A, one influenza with upper respiratory tract infection, two viral infections not specified, one viral meningitis and one dengue. Of the 3 on IFNβ1a, one was a diffuse viral myocarditis, one chicken pox and one viral syndrome no otherwise specified. The overall number of SAE of viral infections in the Total DAC HYP database is shown below.

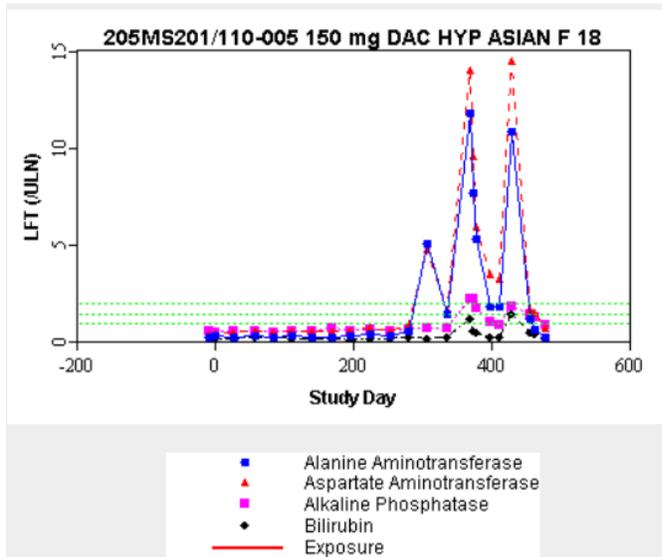
Table 22. SAE Infections, Viral infections HLGT, Total DACHYP database

	Total DAC HYP N=2236 (5214 PYRs)	
Patients with any SAE in this HLGT	13	0.6
VIRAL INFECTION	3	0.1
INFECTIOUS MONONUCLEOSIS	2	0.1
CHRONIC HEPATITIS B	1	0.0
CYTOMEGALOVIRUS INFECTION (CMV hepatitis)	1	0.0
DENGUE FEVER	1	0.0
HEPATITIS A	1	0.0
HEPATITIS C	1	0.0
HERPES ZOSTER/VARICELLA	2	0.0
INFLUENZA	1	0.0
MENINGITIS VIRAL	1	0.0

Source: MO review JUMP. ADAE3, SUR.

A total of 13 patients were diagnosed with SAE of viral infections in the DAC HYP database, including hepatitis A, B, C, mononucleosis, CMV, VZV. Approximately half of those infections were considered severe. One led to drug withdrawal and two to treatment interruption. These viral infections occurred after nine to 76 doses of DAC HYP. The earliest, after 9 doses, was chronic hepatitis B; the latest, after 76 doses was a case of facial herpes zoster.

The case of CMV infection (201/110-005) was consistent with viral reactivation after 13 doses of DAC; a liver biopsy showed CMV viral antigen, serology showed positive IgG and IgM. This was a complex case in a patient who was very sick, with multiorgan involvement and a clinical picture consistent with systemic lupus erythematosus or malignancy. She had elevated liver enzymes and a positive ANA 1:1280. Treated with methylprednisolone, ganciclovir, chloroquine and antibiotics. Liver enzymes came down to normal 5 months after DAC discontinuation but she was subsequently **lost to follow up**. See extended narrative in Section 0 of this review. The course of liver enzymes in this patient is shown below.



It would have been desirable that this patient had longer follow up. It is possible that liver enzymes increased again after Day 480. I believe this case is consistent with DRESS. CMV and other herpes viruses reactivation has been described in patients with DRESS.

The cases of infectious mononucleosis (202/500-009 and 203/508-013) occurred after 21 and 53 doses of DAC HYP respectively, but none of them were IgM+, I am not persuaded that they represent acute mononucleosis or viral reactivation, perhaps these are cases of DILI. An additional case of acute viral hepatitis B was reported after the cutoff of the SUR. Narratives for these cases as well as listings and narratives of other viral infections are included in Appendix 13.3.10 of this review.

Although coded under viral infections, I believe that the following case is consistent with an immune mediated process.

202/363 008 - ASEPTIC MENINGITIS (mentioned under General Disorders SOC, because of SAE of pyrexia). 27 M. He received 13 doses of DAC 150 in 201 and started placebo in 202. Approximately one month after last dose of DAC HYP in study 201, the patient was diagnosed with aseptic meningitis, hospitalized for one week and treated empirically with IV acyclovir and antibiotics. CSF showed 309 cells/mL (normal up to 5), 3 RBC, protein of 1090 mg/L (normal up to 450). An MRI showed new lesions compatible with MS or lymphoma. At that time a skin biopsy showed “subacute eczema”. The event improved but the most recently available CSF still had elevated WBC and protein. The event of meningitis was reported as resolved on Day 420 of study 202. Decreased visual acuity of the right eye was reported at the end of study visit, 4 months after the onset of meningitis, perhaps a sequela of meningitis. DAC antibodies and neutralizing antibodies were transiently positive (unclear clinical significance). *This case could be consistent with immune mediated meningitis and should be included under the Immune*

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system SOC. *A case of aseptic (“lymphocytic”) meningitis has been reported in association with pneumonitis and hepatitis in study 1012 with DAC Penzberg (See 13.3.19)*

In summary, the overall risk of serious infections in the total DAC database was 4.5%. DAC HYP increased the risk of serious infections as compared to placebo (2.9% vs. none in study 201) and to IFNβ1a (4.6% vs. 1.5% in study 301) including bacterial and viral infections. The exact number of opportunistic infections in this database is difficult to assess but there are 2 SAE of Hepatitis B, 1 CMV, and 2 EBV and at least one SAE of TB.

Additionally, there are 3 cases of aspiration pneumonia (2 described under deaths), 3 of urosepsis and at least 3 cases of life-threatening multiorgan involvement suspected to be sepsis without an identified organism consistent with an immune mediated systemic inflammatory response with features that overlap with DRESS. There is also one case of CMV infection and one of brucellosis, with multiorgan involvement suggestive of DRESS (CMV infection does not rule out DRESS; the diagnosis of brucellosis is not adequately supported). The case of adult Still’s disease requires longer follow up.

- **SAE in the Injury, poisoning and procedural complications SOC**

There was no imbalance in the number of SAE in these SOCs in studies 201 and 301 (See table of SAE in these SOCS in all three pools in Section 13.3.3 of this review). Overall, 26 patients presented one or more SAE events in this SOC, including 18 who had one or more fractures after a mean of 60 doses (median 50, range 3 to 146 doses). Six had a reported AE of fall, three had a road traffic accident.

Fall and fractures are not unusual in patients with MS. There are no calcium, phosphorus or magnesium measurements in the protocols to evaluate whether fractures were related to abnormalities on these measurements.

- **SAE in the Metabolism and nutrition disorders SOC**

No imbalance in this SOC in study 201. Four patients in the Metabolism and nutrition disorders presented SAE in the DAC HYP 150 group (0.4%) as compared to none on IFb1a in study 301. One patient had dehydration in association with toxic hepatitis (301/110-006); one had “tetany” after 36 doses of DAC associated with influenza (301/663-007), one had hypokalemia after 12 doses of DAC along with vomiting, diarrhea and MS relapse (301/141-009) and one diabetic ketoacidosis (301/327-005). Additionally, one patient reported obesity and transient hyperglycemia (302/152-502), and one had diabetes mellitus (303/438-001). None led to drug discontinuation. SAE of diabetes mellitus and ketoacidosis were previously discussed under Endocrine disorders.

- **SAE in the Musculoskeletal and connective tissue disorders SOC**

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No SAE occurred in this SOC for DAC in study 201. Six subjects (0.7%) had SAE in DAC150 and 3 (0.3%) on IFNβ1a in study 301. SAE on DAC150 included two potentially immune-mediated events (lupus-like syndrome and spondyloarthritis) that did not occur in IFNβ1a.

A total of 16 patients reported events in this SOC in the total DAC HYP experience as of the SUR. An additional case of inflammatory arthritis was reported after the cut-off of the SUR. A summary of SAE in this SOC is shown below.

Table 23. SAE in Musculoskeletal and Connective Tissue disorders Total DAC HYP, SUR

	ANY DAC Dose N=2236	
	16	0.7
Any SAE in this SOC		
ARTHRALGIA	1	<0.1
BACK PAIN	3	0.1
BURSITIS	1	<0.1
INTERVERTEBRALDISC DISORDER/PROTRUSION	4	0.2
LUMBAR SPINAL STENOSIS	1	<0.1
LUPUS-LIKE SYNDROME	1	<0.1
OSTEOARTHRITIS	1	<0.1
PLICA SYNDROME	1	<0.1
ROTATOR CUFF SYNDROME	1	<0.1
SPINAL OSTEOARTHRITIS	1	<0.1
SPONDYLOARTHRITIS	1	<0.1
TENDONITIS	1	<0.1

Selected narratives are included below.

301/482-005 – 50 F, diagnosed by a dermatologist as **lupus-like syndrome** on Day 701 of study 301 after 24 doses of DAC150. It was severe, led to drug withdrawal and is listed as not resolved, thought to be related to study drug. She initially presented a cutaneous lesion and erythema of the right elbow (b) (6) that worsened and extended to rest of the body, with vesicles and ulcerations. One month and ½ later she developed myalgia, arthralgia and **swelling of wrists**. The skin biopsy showed non-specific inflammatory pathology, but it did not look like cutaneous lupus. WBC with differential was normal, as well as the urinalysis and CRP level. Lupus anticoagulant was negative. ANA, DsDNA. Anti-SS/A and B were negative. A cortisol test showed low basal cortisol and cortisol stimulation consistent with partial adrenal insufficiency. The last dose of DAC was given on (b) (6) (Day 645). Cortisol levels improved by March 2014. In April 2014 the investigator noted papules redness and swelling in

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the proximal phalangeal joints of both hands. Further follow up was scheduled but results are unknown. On July 2014 she developed pruritus and urticarial exanthema on arms shoulders and legs. Dermatologist suspected a viral infection. The event of lupus-like syndrome was considered improved but not totally resolved.

I would agree that this patient had a “lupus-like syndrome” but this is not true systemic lupus erythematosus. There was no hematologic or renal involvement; there was no serologic evidence of SLE. The event was also coded as adrenal insufficiency. The lab and clinical picture is rather consistent with a mixed connective tissue disease or adrenal insufficiency. Either diagnosis is a potential manifestation of a DAC induced immune mediated disorder.

301/604-006 – 52 F developed spondyloarthropathy after 51 doses of DAC HYP 150. She had a history of psoriasis, hyperthyroidism and thyroidectomy. She started DAC HYP on (b) (6) On January 2012 she had exacerbation of prior psoriasis. On (b) (6) (Day 543) she presented generalized pain on all joints suspected to be psoriatic arthritis but X-rays did not confirm psoriatic arthritis. Serious spondyloarthropathy was reported, which resolved on Day 546. Later on an event of erythema annulare was reported (day 628 to 671). Daclizumab was continued, the patient completed the study.

In my opinion this is potentially related to DAC in a patient with predisposition to autoimmunity.

303/645-015*. (15-day report 2015BI155468) 43 F diagnosed with Adult onset Still’s disease Discussed under sepsis of unknown origin.

303/658-012*. (15-day report 2015BI139260) 24 year old female received 22 doses of DAC in 301 and 7 doses in study 303; last dose was on September 2015 (estimated total number of DAC HYP: 29 doses). Since (b) (6) she was admitted to the hospital three times with polyarthritis, later changed to non-specific oligoarthritis. She had pain and swelling of the left ankle since March 2015. This was initially thought to be traumatic but then she also had morning stiffness, pain and swelling of the left knee, arthralgia, back pain and was unable to walk because of pain and body stiffness. She later developed a rash diagnosed as atopic dermatitis. MRI showed no sacroileitis. HLAB27 negative. Serology was negative for autoimmune diseases and infections; repeated arthrocentesis did not grow any organism. She had repeatedly elevated CRP and ESR (up to 110 mm/h). She was treated with doxycycline, prednisone and sulfasalazine. Event is ongoing.

This case is consistent with inflammatory arthritis, and is potentially related to DAC HYP.

- **SAE in the Neoplasms SOC**

There were few SAE in this SOC in study 201 (a total of 4), including two cases of melanoma in the DAC 300 group.

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In study 301, the number of patients with events in this SOC was balanced (1.2-1.5%). There was one case of melanoma in a patient taking IFNβ1a, and no cases on DAC HYP 150. Two benign salivary neoplasms occurred in the DAC treatment group.

Overall, there were 30 cases SAE of neoplasms with an overall incidence of 1.3% in the Total DAC database. A summary table of patients with SAE in Neoplasms SOC for the Total DAC experience by HLGT as of the SUR is shown below.

Table 24. SAE in Neoplasm SOC, by MedDRA HLGT in Total DAC HYP experience.

	N=2236 (5214 PYRs)	
	n	%
ANY neoplasm	30	1.3
BREAST NEOPLASMS BENIGN (INCL NIPPLE)	2	0.1
BREAST NEOPLASMS MALIGNANT AND UNSPECIFIED (INCL NIPPLE)	5	0.2
CUTANEOUS NEOPLASMS BENIGN	1	0.0
ENDOCRINE NEOPLASMS MALIGNANT AND UNSPECIFIED	2	0.1
GASTROINTESTINAL NEOPLASMS BENIGN	2	0.1
GASTROINTESTINAL NEOPLASMS MALIGNANT AND UNSPECIFIED	1	0.0
MISCELLANEOUS AND SITE UNSPECIFIED NEOPLASMS BENIGN	2	0.1
MISCELLANEOUS AND SITE UNSPECIFIED NEOPLASMS MALIGNANT AND UNSPECIFIED	1	0.0
NERVOUS SYSTEM NEOPLASMS BENIGN	1	0.0
NERVOUS SYSTEM NEOPLASMS MALIGNANT AND UNSPECIFIED NEC	2	0.1
RENAL AND URINARY TRACT NEOPLASMS MALIGNANT AND UNSPECIFIED	1	0.0
REPRODUCTIVE NEOPLASMS FEMALE BENIGN	5	0.2
REPRODUCTIVE NEOPLASMS FEMALE MALIGNANT AND UNSPECIFIED	3	0.1
SKIN NEOPLASMS MALIGNANT AND UNSPECIFIED	2	0.1

FDA MO JUMP analysis ADAE3 datasets submitted with SUR.¹⁵

As of the SUR, there were a total of 15 non-benign neoplasms in this database of 2236 patients including 5 cases of breast cancer and no cases of lymphoma. Subsequent to the cutoff of the SUR, 4 additional cases of breast cancer, including one in a male patient and four cases of lymphoma were reported. A summary of SAE by PT in this SOC in the controlled studies is included in Appendix 13.3.3 of this review. The full listing of patients with SAE in this SOC in the Total DAC database as of the SUR is included in Appendix 13.3.12 of this review. Breast cancer and lymphoma are discussed below.

Breast cancer

¹⁵ 11 of 922 (1.2%) IFNβ1a subjects had SAEs in this SOC but none were the same as in the DAC 150 group in Study 301.

As of the SUR, there were 3 breast cancer NOS, one invasive ductal breast cancer, and one “metaplastic” breast cancer. They were all female, ages 45 to 52, diagnosed 350 to 1980 days since starting DAC HYP. Four out of five events were considered not related to study drug and reported as “not resolved”. Four of the five led to drug withdrawal, and two are reported as “no action taken with drug”. The “metaplastic cancer” was considered related to study drug and “resolved.”

There is no such cancer as “metaplastic” cancer. This probably refers to a metastatic cancer. However, it is unlikely that a metastatic cancer could be “resolved”, since it is an incurable disease.

One breast cancer in a male subject was reported after the SUR, as follows.

303/115-006* (2015BI149665, November 2015). 59 M. Received 36 doses of DAC150 in study 301 and an unknown number of doses in 303 for a total of 4 and ½ years of treatment. At the time of the event he had a diagnosis of suspected contact allergic dermatitis, treated with prednisone 10 mg/day. He also had edema of the legs and vasculitis (not reported location or duration). In (b) (6) he was found to have a breast nodule (approx. 0.5 cm). A biopsy showed invasive intraductal carcinoma and Paget’s disease of breast. In retrospect, he had noticed the nipple lesion for a few months prior this diagnosis. The investigator attributed the male breast cancer to DAC. I agree. As per a follow up safety report (January 2016) the patient underwent right breast mastectomy. The tumor was a well differentiated 5 cm intraductal carcinoma in situ with pagetoid changes, ER+ PR+ HER-2 negative. Sentinel biopsy was negative. DAC HYP had been discontinued in April 2015 because of a skin reaction. *Breast cancer is a prevalent disease in females, but very rare in males. Information from the NCI Surveillance Epidemiology and End Results Program (SEER) is shown below.*

Table 25. Incidence rate of breast cancer (invasive) in the US as per SEER¹⁶

Age-adjusted SEER Incidence^a Rates by Year, Race and Sex

Year of Diagnosis	All Races		
	Both Sexes	Males	Females
1975-2012	68.95	1.11	125.85

Age-adjusted SEER Incidence^a Rates by Year, Race and Age

Year of Diagnosis	All Races, Females		
	All Ages	Ages <50	Ages 50+
1975-2012	125.85	43.46	341.59

SEER 9 areas (San Francisco, Connecticut, Detroit, Hawaii, Iowa, New Mexico, Seattle, Utah, and Atlanta). Rates are per 100,000 and are age-adjusted to the 2000 US Standardized.

¹⁶ SEER NCI. Surveillance Epidemiology and End Results Program. Cancer statistics. Population http://seer.cancer.gov/csr/1975_2012/browse_csr.php?sectionSEL=4&pageSEL=sect_04_table.08.html

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As per SEER, the overall incidence rate of invasive breast cancer in the US regardless of gender is 69 per 100,000 population per year, but it is much higher in female (125.85 per 100,000 population per year) than in male (1.11 per 100,000 population per year), and varies greatly with age (from 43 per 100,000 for female <50 to 343 per 100,000 for female ≥50 years.)

As per response submitted on February 8, 2016, there were 3 more cases of breast cancer in female patients, for a total of 8 female breast cancers, therefore $8/4311=185$ per 100,000 PYRs. Assuming that the risk of breast cancer is similar in US and non-US populations, the rate of breast cancer in the DAC database is higher than the background population (all ages) and is particularly high for younger ages (there were no patients older than 55 years at entry). The incidence of male breast cancer in the DAC database as of December 21, 2015 is 0.1% (1/751) or 43 per 100,000 PYRs (1/2323 PYRs) is greater than the rate in the background population for males of all ages (1 per 100,000 population).

One of those female breast cancers was reported on January 2016 in a patient who had been previously suspected to have lymphoma. Patient 203/500-003 51 F diagnosed with breast cancer in September 2015 with R breast mastectomy (b) (6). There were 3/21 metastatic lymph nodes and 18/21 were reactive lymph. ER+ PR+ Her-2 negative. Last dose of DAC was in October 2014. *Although DAC HYP was stopped almost a year prior to the diagnosis, the fact that there are still "reactive" lymph nodes suggests that DAC HYP may potentially have persistent immunologic effects beyond 6 months.*

Lymphoma

No cases of lymphoma had been reported in the daclizumab database as of the SUR. Four non-Hodgkin's lymphomas (NHL) were reported after the cut-off of analyses of the SUR and therefore they are not in Total DAC HYP experience tables. Two of them were discussed in the SUR (but again, not included in the ISS analysis) and two were reported as 15-day safety reports. The cases are as follows. One patient had been treated for 1.5 years, one approximately 4 years, one for >4 years, but unclear duration of therapy, and one for 7 years.

303 678-004* 36 M. received IFb1a in 301 and DAC HYP 150 in 303 (number of doses unknown). Onset was 560 days after the first dose in study 303. Last dose was Feb 11, 2015 (approx. 1 and ½ years of DAC). Since Dec 2014 he noted cervical lymphadenopathy. On (b) (6) lab tests were within normal except for elevated monocytes (11.55, normal up to 10%) and slight elevation of uric acid. "Immunology testing" was negative (unclear what exactly this entailed). CT scan showed multiple adenopathy on the superficial and deep cervical occipital and supraclavicular and axillary chains bilaterally. (b) (6) biopsy of 2 cervical ganglia favored "partial (~30-35%) lymphoganglionic infiltration of grade 3A follicular, B-cell non-Hodgkin's malignant lymphoma." Bone marrow biopsy was done (b) (6) did not show lymphoma of the BM. The investigator considered the event not related to DAC.

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*I believe that given the immunosuppressive and immunologic effects of DAC HYP it is conceivable that DAC played a role in the emergence of NHL (1 and 1/2 years into treatment). In a follow up submission the applicant stated that an independent hematopathologist did not find “unequivocal evidence of a non-Hodgkin’s B or T lymphoma.” However, Tcell rearrangement detected a **monoclonal population**. The histopathological and immunohistochemical appearance, along with monoclonal proliferation are consistent with malignant lymphoma. Moreover, on follow up the patient was treated with RCHOP starting in June 2014.*

203/500-003* 51 F from Poland. Lymphadenopathy was reported after the SUR data cut-off. It was initially reported as “peripheral Tcell lymphoma unspecified” based on the local histopathological examination. The patient received DAC HYP from August 2010 to October 2014. She presented lymphadenopathy in November 2014 (it is unclear if reports refers to days in study 203 or from the beginning of 201). A biopsy was done [REDACTED] (b) (6). As per the CIOMS form, the pathology report revealed; cervical lymph node of blurred structure with infiltration of small polymorphict-lymphocytes with the following immunophenotype: cd3+, cd4+, cd8+, cd7+ in some of the cells, cd5+, tdt-, cd30+ in single cells and cd20-, cd23- (remains of disorganized dendritic cell network were visible). MIB (+) in approximately 30% of cells was observed. A diagnosis of peripheral t-cell lymphoma not otherwise specified (PTCL, NOS) was made. Study medication was discontinued. As per a response submitted on July 2015, an independent expert hematopathologist reviewed the results of additional histomorphological and molecular diagnostics and a diagnosis of lymphoma was not supported because of the absence of clonality and negative Tcell receptor gene rearrangement. The case is currently being followed up and the subject is reported to be in good clinical condition with reported *regression of the lymphadenopathy following the discontinuation of the study treatment*. Upon an FDA request for additional information, the applicant stated that the patient remains untreated while waiting for the results of additional analyses conducted in the US. The sub-investigator reported, during a phone call to the site, that the lymph nodes that were palpable previously were getting smaller in size and the patient’s overall condition continued to be good. A follow up CT scan was scheduled for November 2015.

As per follow up IND safety report in January 21, 2016 (2015BI131493) the patient was not treated for lymphoma but was diagnosed with metastatic breast cancer on September 2015 (*mentioned early under breast cancer*).

203/761-004* 44 M. B cell lymphoma. Submitted as a 15-day safety report on August 19, 2015. Medical Hx of tuberculosis of left lung (partial resection of left lung). No concomitant meds. First dose was May 2011. He has received 52 doses in 203. Last dose was April 14 2015. A FNA of cervical (supraclavicular and submandibular) lymphadenopathy [REDACTED] (b) (6) showed lymphoproliferative disease. LN biopsy scheduled by oncologist [REDACTED] (b) (6) showed lymphoma. As per follow up information submitted on 9/25/15, the patient was hospitalized [REDACTED] (b) (6) and is being treated with radiation therapy.

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Immunohistochemistry showed that tumor cells were positive for: “CD20, [illegible] 5, CD10, all 2+/- and negative for: CD5, CD23 (positive in dendritic cells), all 6, Cyclin D, Ki67 – 20%. The staining was most pronounced on the periphery. According to the physician’s opinion, the finding was follicular lymphoma (G=1). There was no bone marrow involvement. In a follow up IND safety report (October 2015), the investigator reported that the patient is now being treated with rituximab.

Of note, an external hematopathologist consulting for Biogen/Idc believes this is “florid reactive follicular hyperplasia (B-cell hyperplasia)” without evidence of lymphoma. Regardless of the opinion of the external pathologists, the patient is now being treated for lymphoma. This case should be counted as lymphoma.

203/453-003* 59 F, participated in study 201, 202 and 203 for a total of 7 years. In (b) (6) noted growing axillar lymphadenopathy, followed by cervical and supraclavicular lymphadenopathies of 3 to 6 cm, accompanied by night sweats and 3 Lb. weight loss over one month. A biopsy showed T cell lymphoma. Biopsy was referred to an external expert for second opinion. As per additional information submitted on October 16, 2015, Serology indicated prior infection with EBV, no evidence of acute infection. Hepatitis and HIV testing were negative. She was diagnosed with peripheral T cell lymphoma and treated with cyclophosphamide, doxorubicine, vincristine, prednisone and etoposide (CHOEP). Drug was discontinued (last dose (b) (6)).

The external hematopathologist consulting for Biogen Idc reviewed the available data and believes that there was no convincing evidence of T cell lymphoma. He found atypical paracortical T cell and histiocytic hyperplasia; EBV positive cells, consistent with EBV infection. Again, regardless of the consultant’s opinion, this event is being aggressively treated as lymphoma and should be counted as lymphoma in the adverse event analysis.

In summary, 4 patients with diagnosed with non-Hodgkin’s lymphoma in this application. All four after the cut-off of the SUR. All cases discontinued DAC HYP. Three of them are ongoing oncologic treatment and one is getting better (smaller adenopathies) after DAC HYP discontinuation. *At least 3 were treated as NHL among 2236 patients (5214 PYRs) exposed equals 58 per 100,000 PYRs, which is greater than the background population for ages <65 in the US Surveillance, Epidemiology and End Results Program (SEER). (9.3 per 100,000 per year)*

Table 26. Lymphoma, incidence rate per 100,000 population per year (SEER¹ 2007-2011)

2007-2011
Under 65 and

Source: Table 19.7 and 9.7 of Cancer Statistics Report accessed April 28, 2014. Age-adjusted to the 2000 US Standard Population in the US. Extracted by FDA medical officer from SEER online data.

1 http://seer.cancer.gov/csr/1975_2011/browse_csr.php?sectionSEL=19&pageSEL=sect_19_table.07.html#table2

A review of the literature by this MO did not support an increased risk of lymphoma in patients with MS as compared to the general population. Additional malignancies are discussed in Appendix 13.3.12 of this review.

Summary regarding malignancies in DAC database: In general the types of cancer in this application are heterogeneous and appear to be within the type presented in the general population. The database is relatively small and short to assess the risk of malignancies. However, there are at least three cases of lymphoma (plus one case that is regressing off drug). Regression of lymphoma is not unusual after discontinuation of immunosuppressor therapy. Additionally, there are nine cases of breast cancer (including one male patient). The rate of breast cancer and NHL with DAC HYP is greater than the background population. Immunosuppressors are known to be associated with long term risk of malignancy. The number of lymphomas and breast cancers in this database exceeds the rate in the background population for this age. If approved this should be included in labeling. It is unclear what type of advice could be given to patients to decrease the risk of breast cancer, particularly in male patients.

- **SAE in the Nervous system disorders SOC**

SAE in the Nervous system disorders not reported as MS/MS relapse or progressive MS in the controlled studies are summarized below and listed after the table.

Table 27. Patients with SAE in Nervous system disorders SOC not reported as MS relapse, studies 201 and 301

Study 201			Study 301	
DAC150	DAC300	Placebo	DAC150	IFNb1a
N=207	N=208	N=204	N=919	N=922
1 (0.5)	3 (1.4)	1 (0.5)	14 (1.5)	7 (0.9)

Excluding MS relapse, SAE on DAC included one syncope, one migraine, one intracranial aneurysm on DAC 300, and one cerebrovascular insufficiency in DAC 150. The case of syncope was in a patient with an acute hypersensitivity reaction that led to drug discontinuation (see Immune mediated disorders). There was one SAE on placebo (temporal epilepsy).

In study 301, excluding MS relapse, there were 14 and 7 events in the DAC150 and IFN groups, respectively. The listing of these patients is included below.

Patients with SAE not reported as MS relapse in study 301

On DAC150

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116-001	MIGRAINE
123-009	COMPLEX PARTIAL SEIZURES
125-005	CONVULSION
133-004	HEADACHE
141-009	UHTHOFF'S PHENOMENON
161-004	TOXIC ENCEPHALOPATHY
407-001	DIZZINESS
544-013	CONVULSION
600-010	MYASTHENIA GRAVIS
600-017	STATUS EPILEPTICUS
608-007	CONVULSION
612-010	SCIATICA
617-004	CONVULSION
629-008	TRANSIENT ISCHAEMIC ATTACK
On INFβ1a	
459-003	TRIGEMINAL NEURALGIA
514-005	CONVULSION
604-015	MUSCLE SPASTICITY
604-037	EPILEPSY
604-065	TENSION HEADACHE
610-007	OPTIC NEURITIS
617-008	SPEECH DISORDER

In study 301, there were more serious seizures on DAC150 (n=6 [0.7%], including 4 convulsions, 1 status epilepticus and one complex seizure) as compared to IFNβ1a (n=2 [0.2%], one convulsion and one epilepsy). This analysis is supported by an excess of seizure-related events among all (serious and non-serious) events in the Seizures HLGT in study 301.¹⁷ Review of SAE of seizures did not identify any particular pattern/cause for seizures.

Analyses by HLGT in the Nervous system disorders SOC in the Total DAC experience are shown in the following table.

Table 28. SAE by HLGT in the Neurologic disorders SOC in the Total DAC database

¹⁷ Patients with all serious and non-serious AE of seizures in study 301: 11 (1.2%) DAC150 treatment group and 3 (0.3%) in the IFN group.

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	Total DAC HYP N= 2236	
	n	%
ANY SAE IN NEURO SOC	274	12.3%
ANY SAE except demyelinating disorder	31	1.4%
DEMYELINATING DISORDERS (includes MS and MS related terms)	248	11.1
SEIZURES (INCL SUBTYPES)	10	0.4
CENTRAL NERVOUS SYSTEM VASCULAR DISORDERS	5	0.2
NEUROLOGICAL DISORDERS NEC	5	0.2
HEADACHES	4	0.2
INCREASED INTRACRANIAL PRESSURE AND HYDROCEPHALUS	1	0.0
NEUROMUSCULAR DISORDERS	1	0.0
PERIPHERAL NEUROPATHIES	1	0.0
ENCEPHALOPATHIES	1	0.0
SPINAL AND NERVE ROOT DISORDERS	1	0.0

FDA MO JUMP analysis. ADAE3 SUR. Generated manually.

In study 201, episodes of MS relapse were reported as adverse events at the investigator's discretion. In study 301 the protocol instructed that all episodes of MS/MS relapse were to be reported as adverse events. Adverse events of MS relapse will not be reviewed in this review. I will focus on neurologic events not reported as MS relapse, although some of these events may have been related to MS. Of note, there were SAE of 10 seizures in the total DAC HYP database. Individually, it is difficult to attribute the cases to DAC, but given the excess compared to IFN, and the fact that IFN already carries a warning for seizures, I conclude that DAC HYP increases the risk of seizures in patients with MS.

A listing of patients with SAE in this SOC not reported as MS relapse in the Total DAC HYP database is included in Appendix 13.3.13 of this review along with narratives of seizures and other non-MS relapse events. Selected narratives for SAE in the Nervous system disorders SOC are included below.

202/509-014, 40 F – Demyelination, diagnosed Central Pontine Myelinolysis (CPM). Patient received placebo in 201 and 13 doses of DAC HYP 300 in study 202 (last dose was on Day 339). Medical history included impaired concentration, bladder incontinence, emotional lability, depression, unsteady walking. She had at least one episode of MS relapse in 201. Cognitive disorder was reported as a non-SAE on day 228. Dyskinesia/involuntary movements were reported on Day 219 and 224. She was hospitalized with “mental disorder due to psychoorganic syndrome” on Days 228-241. On Day 241 of study 202, she had MS progression.

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Cachexia was reported on day 310. During study 202 (b) (6) had non serious AE of erythema of skin of neck and throat. Liver US showed focal steatosis. In (b) (6) she was diagnosed with folate deficiency. On day 353 she was diagnosed with CPM. There is no end date for this event. A “multifocal demyelinating disease of the CNS” was reported on Days 374, “causing psychoorganic syndrome.” A mild rash of face and neck was reported in July 2011. Dehydration was reported on Day 416. Concomitant meds included doxepin for depression, IV MP for MS. The patient had a lumbar puncture for cognitive impairment (b) (6) that showed clear CSF and was negative for JC Virus. Labs showed high platelets from screening in study 201. Her EDSS score went from 4 at screening in study 201 to 8 at weeks 44, 52 and 72 of study 202 (Days 310, 366 and 506, respectively). The event of “demyelination” was considered resolved with sequelae of psychoorganic syndrome on June 2011.

*This is an odd case. The number and size of MRI lesions seem to have decreased but the patient was cognitively worse and also had dyskinesia. Central pontine myelinolysis (CPM) is a demyelinating disorder associated with osmotic stress. Sodium and potassium levels look within normal throughout 201 and 202; it is unclear how the diagnosis of **central pontine myelinolysis** was made. I wonder if this could be MS relapse or some other autoimmune neurologic condition. As per follow up information submitted 3/3/16, the investigator’s diagnosis was made on the basis of MRI findings showing central myelinolysis in pons and demyelinating plaques in both hemispheres. The subject’s sodium levels were between 138 and 146 mmol/L throughout the study. The AE of osmotic demyelination syndrome does not have a reported outcome; the SAE of demyelination is reported as resolved with sequelae on 03 Jun 2011 (DAC Day 361). The subject completed the study on 26 Oct 2011 (DAC Day 506). There is still insufficient information to confirm a diagnosis of CPM.*

303/611-015 36 year old M presented epilepsy after a total of 43 doses of DAC150. During study 301 he had three episodes of MS relapse. He had “non-protocol defined MS relapse” in study 303. His family noted disturbances of cognitive functions, confusion and swallowing difficulties. From screening to end of study 301 the patient lost almost 40 Lbs. of weight. MRI showed **tumor-like demyelination** and progressive demyelinating disease. CSF was non-diagnostic. He had a weak positive ANA. Other autoantibodies were not detected. He was discharged home “on stable condition” (b) (6) Treatment included levetiracetam, MP and potassium. His final dose of DAC HYP was (b) (6) (Day 168 of study 303). His EDSS score went from 1.5 at baseline in study 301 to 3.0 on the last day of study 301 (first day of study 303). On Day 222 of study 303 (May 2014) his EDSS score was 4.5 and he started IFNβ as alternative MS medication. In (b) (6) he presented another SAE of non-protocol defined MS relapse. The event was reported as resolved on Day 413 of study 303. Three months after the last dose of DAC HYP) he was admitted to the ICU with respiratory failure, aspiration pneumonia and septic shock. Transferred to the ICU, had mechanical ventilation and eventually required a tracheostomy. The events resolved (b) (6) At that time he had an EDSS of 9. Natalizumab was started. Current status is unknown.

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It is impossible to distinguish whether this is MS progression or some other process, including the possibility of a DAC HYP induced demyelinating disease. As per follow up submitted on 3/3/16, this patient is no longer participating in Study 205MS303. The AE of aspiration pneumonia began on (b) (6) (study Day 1284) and resolved on (b) (6) (study Day 1399). The subject withdrew consent on 27 Feb 2015 (study Day 1515) due to insufficient efficacy (MS relapses during IP treatment).” The last dose of DAC had been in March 2014.

303/600-010 51 M. **Myasthenia Gravis (MG)**. He received DAC 150 in study 301, and one additional dose of DAC 150 in study 303. In 301 he had MS relapse on Day 994 to 997. On day 997, MG was reported, which was not resolved and was ongoing at baseline in 303. The same day, a Tolosa Hunt syndrome (superior orbital fissure syndrome) was reported, with suspected sphenoiditis, treated with antibiotics. On Day 18 of study 303 MG of moderate intensity was reported again, with end on Day 182. MG was treated with IV MP for 3 days and neostigmine followed by prednisone and pyridostigmine and ambenonium. Depression and dysphagia, global weakness and drooping of eyelids (right greater than left) were also reported on Day 18. No further doses of DAC were given. Anti-acetylcholine receptor and anti-muscle-specific tyrosine kinase (MuSK) antibody tests were negative. A non-serious AE of mediastinal neoplasm and streaky fibrosis of the right lung were reported on Day 20 to Day 177 of study 303. A diagnosis of a suspected thymoma was made. Peripheral motor neuropathy was reported on Day 36, based on electromyography. The event did not resolve. On (b) (6), a cerebrospinal fluid (CSF) test showed poorly delineated oligoclonal Type 2 IgG bands. On (b) (6), MRI of the head showed small post-inflammatory demyelinating lesions without signs of active demyelination.” She was discharged with diagnosis of MG. At the last follow up the patient was still taking prednisone 40 mg /day. The patient had a 5 kg weight loss between the baseline measurements in studies 301 and 303. Her EDSS went from 3.5 at baseline in 301 to 4.5 at baseline in 303. Atrophy of small muscles of the right upper extremity and of right lower extremity were noted at the early termination visit. Anti DAC antibodies were negative at all times. On (b) (6), the subject underwent a thymectomy. *This is antibody negative Myasthenia Gravis (MG). She responded to corticosteroids and neostigmine and stabilized after thymectomy. Atrophy on the small muscles on the right upper and lower extremity is not typical of MG. On September 28, 2015 DNP requested the pathology report. As per follow information submitted 3/3/16, no formal pathology report was produced for the subject’s thymectomy due to poor specimen quality but based on histology, there was no feature of thymoma. The investigator confirmed that no genetic testing was done and that the event of MG did not resolve. Given the immunologic effects of DAC HYP, I believe it may have played a role in the development of MG, although I am not that clear that this was in fact MG.*

303/659-001 29 F. Seizure and **Cerebral venous thrombosis** in patient with recent diagnosis of sarcoidosis. She received 36 doses of DAC HYP 150 in study 301 and three additional doses in study 303. Presented alopecia and erythema nodosum from Day 820 to 967. EDSS went from 1.0 at baseline in 301 to 4.0 at week 144 of 301. In study 303 erythema nodosum, pneumonia and oral candidiasis were reported within the first 4 weeks of study, and a non-serious event of

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moderate sarcoidosis was reported on Day 83, leading to drug withdrawal. Concomitant meds at the time of diagnosis of sarcoidosis included escitalopram, gabapentin, paracetamol and trazodone. She was treated with methylprednisolone 48mg orally from Day 82-201 and lansoprazole. No biopsy was reported. At some point, oral contraceptive was started (levonorgestrel/ethinylestradiol). She had received 3 doses of DAC HYP in study 303; the last dose was on Day 57 (b) (6). On day 107 of study 303, she presented cerebral venous thrombosis (serious) and generalized tonic clonic seizures (non-serious). She was treated with fraxiparine, levetiracetam and methylprednisolone, and contraceptive was stopped. Event of cerebral venous thrombosis is reported as ending on Day 127. Antiphospholipid antibodies are not mentioned. Suspected etiologies for the event of cerebral venous thrombosis were hormonal pills and sarcoidosis for which the subject received corticosteroid therapy. Last dose of DAC was on Day 57; stopped because of “progression of sarcoidosis.”

I agree that the venous thrombosis might be related to oral contraceptives and underlying sarcoidosis. It is unclear whether there were any lab abnormalities preceding the event of thrombosis. There was limited information about the sarcoidosis event. In response to a request for information the applicant clarified that the patient had dyspnea and a CT scan of the chest that showed confluent, indistinct nodulation (size approx. 15 mm) at the bases of both lungs, isolated nodules of up to 5 mm in lower legs and multiple mediastinal lymph nodes up to 11 mm, in the aorto-pulmonary window and hilar nodes up to 7 mm. A pulmonologist diagnosed sarcoidosis based on the lung nodules, mediastinal lymph nodes and cutaneous erythema nodosum. Although there was no biopsy to confirm the diagnosis, I agree with the pulmonologist’s clinical diagnosis of sarcoidosis. Although diagnosed on Day 83 of study 303, the symptoms seem to have started earlier, in 301.

Of note, four patients had SAE of headaches. One patient (301/133-004) underwent a temporal artery biopsy, because of suspected temporal arteritis (TA). As per follow up submitted on 3/3/16, the biopsy did not confirm “active” TA, but the ophthalmologist who evaluated the patient treated her with high dose prednisone, as if she did have TA. *Of note, I identified this case from the concomitant medications dataset. The event of TA is not in the AE datasets.*

Summary of SAE in Nervous System disorders: Evaluation of SAE in this SOC identified an increased risk of seizures with DAC150 as compared to IFN61a. There were two cases of atypical MS relapse one with tumor-like demyelination and one diagnosed as central pontine myelinolysis (without sodium levels). A SAE of Myasthenia Gravis was identified in this database, which required high dose prednisone and thymectomy. The relationship to study drug is uncertain but plausible. One case of cerebral thrombosis was identified in a patient with sarcoidosis. Sarcoidosis could increase the risk of thrombosis. One patient underwent temporal artery biopsy and was treated with high dose corticosteroids because of suspicion of temporal arteritis. Additionally a case of aseptic meningitis was reported under the Infections SOC. In my

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opinion any autoimmune disease observed in this SOC could have been potentially induced by DAC HYP.

- **SAE in Pregnancy, puerperium and perinatal conditions SOC**

There were no imbalances in the number of SAE in the Pregnancy, puerperium and perinatal conditions SOC. There was one missed abortion on placebo in study 201; 4 spontaneous abortions in 301 (3 on DAC 150 and 1 on IFNβ1a). Overall, there were five SAE in 4 patients in this SOC in the Total DAC HYP database. All were severe. As per the datasets only one led to drug withdrawal (202/110-006); as per the narratives, three patients stopped DAC HYP.

The three spontaneous abortions and one ectopic pregnancy were diagnosed at 8-10 weeks gestational age after 8 to 25 doses of DAC. One patient had stopped oral contraception, but contraception failed on the other 3 cases (two including barrier contraception). Two of the patients had a prior miscarriage. No conclusions can be drawn regarding the role of DAC HYP in these events. (Cases are listed in Appendix 13.3 (13.3.14) of this review.)

- **SAE in the Psychiatric Disorders SOC**

There was no imbalance in the incidence of SAE in the Psychiatric disorders SOC in studies 201 and 301. In study 201, there was one event of suicidal ideation on DAC 150 and none on placebo. In study 301, there was one event of suicidal ideation and one suicidal attempt on DAC HYP as compared to one complete suicide, two attempted suicide and one suicidal ideation with IFN. The numbers are small to conclude that there are any differences in the suicidality risk between DAC HYP and INF. SAE in the Psychiatric disorders SOC in the Total DAC HYP database is summarized below.

Table 29. Patients with psychiatric SAE in Total DAC HYP database

	ANY DAC HYP Dose N=2236	
	n	%
Patient with any event in SOC	16	0.7
DEPRESSION	6	0.3
Mental or MOOD DISORDER DUE TO A GENERAL MEDICAL CONDITION	3	0.1
SUICIDE ATTEMPT *	5	0.2
ANXIETY	2	0.1
SUICIDAL IDEATION	1	<0.1
SUBSTANCE ABUSE	1	<0.1
SOMATOFORM DISORDER	1	<0.1

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ACUTE STRESS DISORDER	1	<0.1
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Source: MO analysis ADAE3 SUR. One patient may have more than one event.

Includes one patient who had events in 201, 202 and 203. * Includes case coded as “depression suicidal” and one who had a suicide attempt not entered in dataset (in a patient with depression).

As per the ISS AE datasets, 3 patients had SAE in the Suicidal and self-injurious behaviors NEC MedDRA HLGT among 2236 patients exposed to DAC HYP, including 2 attempted suicide and 2 suicidal ideation. However, two additional patients had suicidal attempts that were not coded as such in the AE dataset (301/128-003 and 203/453-010). The listing of patients with suicidal behavior/ideation is included in Appendix 13.3 (13.3.14) of this review.

SAE of depression occurred in 6 additional patients in this database (301/128-003, 301/130-005, 301/131-003, 302/551-103, 303/438-003 and 303/482-002). They were 5 females, 1 male ages 38 to 51 years, after 1 to 67 doses of DAC HYP 150 (mean: 24 doses, median 18.5 doses). Four had a prior history of depression. No action was taken with DAC.

Cases of depression including suicidal ideation and attempted suicide occurred with DAC HYP. Most were in patients with prior history of depression. In the active controlled trial, the risk of suicidality related events was not different from INF.

- **SAE in Renal and Urinary Disorders SOC**

There was no imbalance in the number of patients with renal and urinary disorders SOC in the controlled trials. In study 301 there were 3 SAE of nephrolithiasis and one of renal colic with DAC HYP as compared to one urinary calculus with INF, suggesting perhaps an increased risk with DAC HYP, but the numbers are small. However, overall number of serious and non-serious events of nephrolithiasis and renal/urinary calculus was similar in both arms.

A total of 11 patients presented SAE in this SOC as of the SUR.

Table 30. Patients with SAE in Renal and Urinary Disorders SOC, Total DAC experience

	Total DAC HYP N=2236	
	n	%
Patient with any event in SOC	11	0.5%
Nephrolithiasis	4	0.2%
Renal colic	2	0.1%
Glomerulonephritis	2	0.0%
Calculus ureteric	1	0.0%
Hydronephrosis	1	0.0%
Mesangioproliferative glomerulonephritis	1	0.0%
Nephrotic syndrome	1	0.0%

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Urogenital fistula	1	0.0%
Vesicoureteric reflux	1	0.0%

Source: MO analysis. ADAE3 SUR. A patient may have more than one event.

Seven patients presented SAE under the Urolithiasis and Urinary tract signs and symptoms HLGTS, including nephrolithiasis, renal colic or ureteric calculus, after 7 to 69 doses of DAC HYP. Dose was interrupted in two and no action was taken with drug with five; all resolved. Cases of urolithiasis/renal colic are listed in Appendix 13.3 of this review (13.3.14).

There might be an increased risk of urolithiasis in patients taking DAC (0.3%) as compared to IFNβ1a (0.1%) in study 301, but the numbers are small. It is unclear whether the risk of urolithiasis is increased in patients with MS as compared to background population. Some patients already had a prior history of urolithiasis. There are no available measurements of calcium, phosphorus or uric acid levels to evaluate whether daclizumab could have an effect on any of these electrolytes.

There were two SAE of glomerulonephritis, after 24 and 68 doses of DAC. Both led to study withdrawal and did not resolve. One was treated with corticosteroids, the other apparently was not. An additional case of glomerulonephritis was reported in a patient with autoimmune hepatitis and thrombocytopenia, but on response to a request for information, the applicant responded that the event of glomerulonephritis was not confirmed. A SAE of renal sarcoidosis was reported in this application after the cutoff of the SUR.

The two confirmed cases of glomerulonephritis and the case of sarcoidosis are described below.

202/505-018 - 20 M, glomerulonephritis, Mesangioproliferative GN and nephrotic syndrome. The patient received 13 doses of DAC 300 in study 201, 11 doses in 202. In (b) (6) after 2 doses in study 202, he presented lower extremity edema; urinalysis showed proteinuria of 240 mg/dl. He was seen by a nephrologist and hospitalized. During hospitalization proteinuria was up to 2.7 g/L, associated with elevated cholesterol. Treated with indapamide, perindopril and simvastatin. He was discharged with proteinuria of 1.4 g/L. DAC HYP was restarted. He was hospitalized again after the 6th dose in study 202. A renal biopsy showed mesangial proliferative GN, segmental and focal lesions. The event was considered not related to drug, and treatment with DAC HYP continued. He was not treated with corticosteroids. In April 2011, after the 11th dose of DAC HYP he was hospitalized again for a second kidney biopsy and evaluation of immunosuppressive treatment. Proteinuria was 1.1 g/L and cholesterol was elevated. He was treated with methylprednisolone, followed by oral prednisone. DAC was discontinued. As per follow up with the investigator, the event of glomerulonephritis was resolved approximately one year later.

Mesangioproliferative GN resolved with corticosteroid treatment approximately 1 year after DAC HYP discontinuation. It is unclear if he was still taking prednisone. The patient underwent

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two kidney biopsies in the process of evaluating this disease that may have potentially been induced by daclizumab.

203/500-002 – 45 M, glomerulonephritis after 68 doses of DAC 150. He received placebo in 201, and DAC HYP 150 in 202 and 203. He had one episode of MS relapse after 4 doses of DAC in study 203 and a SAE of glomerulonephritis in (b) (6), after 42 doses of DAC in study 203. Medical Hx before 201 included hypercholesterolemia. Concomitant meds were baclofen and magnesium. On (b) (6) he showed peripheral edema and high level of proteinuria with initial dx of nephrotic syndrome. On admission to the hospital (Day 1150) he had elevated BP (165/85). Urine protein was 900 mg/dL, the sediment had dysmorphic erythrocytes, microgranular casts and 1-2 hyaline casts. Repeated 24 hour urine showed 13.0 gr per 24 hour excretion. Urine culture was negative. Creatinine and CRP were normal. pANCA and cANCA were negative. CT scan of abdomen showed bilateral cysts up to 24 mm in diameter. A renal biopsy showed 5 completely sclerosed glomeruli and five with segmental sclerosis. There was also focal fibrosis with atrophy of tubules and infiltration of mononuclear cells. Dx was focal segmental glomerulo sclerosis with moderate degree of hyalinization of arteries and arterioles and damage to stroma with chronic changes. Immunofluorescence did not show immunoglobulin or complement deposits. Urine sediment showed epithelial cells and dysmorphic erythrocytes. Treatment included Ramipril, furosemide, hydrochlorothiazide, simvastatin, nadroparin and potassium. Drug was discontinued. The patient was discharged after improvement but the event was ongoing at the time of last follow up.

Patient developed focal and segmental glomerulonephritis with nephrotic range proteinuria after 68 doses of DAC HYP. In the opinion of the investigator this was not related to DAC HYP. In my opinion this condition could be plausibly related to DAC HYP, particularly that it is the second case of nephritis in this database of 2236 patients.

I discussed these two cases with Dr. Evelyn Mentari, a member of the DNP Safety Team and a nephrologist by training. Upon review of the available data she concluded that these cases could be related to DAC. She recommended that if approved or if further trials are planned, urinalysis (with quantitated protein) should be obtained every 3 months. If positive, they should be followed by 24 hour urine collection for quantification of protein and creatinine.

303/325-001* Renal sarcoidosis. As per the datasets, he was a 47 year old M who reported multiple non-SAE in study 301 such as arthralgia (Day 151), mouth ulceration (Day 240), dry eyes (Day 356), visual impairment (Day 447), intermittent symptoms of urinary tract infection starting on Day 147, headaches (since Day 721), viral infection (Day 1013-1020) and lymphocyte decrease (Day 1038-1062). None of these events led to drug WD, although some of them were not resolved at the time of the SUR (e.g. visual impairment). As of the SUR, he had received 36 doses of DAC150. As per information submitted by the applicant on 2/8/16, a SAE of sarcoidosis was reported on Day 1423 of DAC HYP treatment (Day 667 of study 303). He had received a total of 47 doses at the time of the event. His last dose in study 303 had been on

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September 17, 2015. In June 2015, approximately 6 months prior to this diagnosis, the investigator had noted a deterioration of the subject's renal function that was initially attributed to recurrent urinary infections. The patient was evaluated by a nephrologist and underwent a renal biopsy (b) (6). The biopsy showed tubulointerstitial nephritis and granulomatous inflammation consistent with sarcoidosis. He was treated with oral prednisolone (starting dose 75 mg/day). The event is ongoing and the patient is still being treated with prednisolone (unknown dose) 4 months after drug discontinuation.

Reviewer comment: It is unclear as to when the event of sarcoidosis started. It was diagnosed in 303 but some of the symptoms presented in study 301 may have been manifestations of sarcoidosis.

- **SAE in Reproductive system and breast disorders SOC**

There was no imbalance in SAE in the Reproductive system and breast disorders in studies 201 or 301. A total of 24 SAEs in 17 patients occurred in this SOC among 1485 female exposed to DAC HYP 150 or 300 mg. Overall, 1.1% of females had a serious AE in the reproductive system and breast disorders (excluding malignancies).

Table 31. Patients with SAE in Reproductive system and breast Disorders SOC, Total DAC HYP, female patients

	ALL FEMALE on DAC HYP N= 1485	
	n	%
Patients with any event in this SOC among females	17	1.1%
Ovarian cyst	5	0.3%
Endometriosis	3	0.2%
Adenomyosis	3	0.2%
Postmenopausal haemorrhage	2	0.1%
Endometrial hyperplasia	2	0.1%
Dysfunctional uterine bleeding	1	0.1%
Uterine inflammation	1	0.1%
Uterine haemorrhage	1	0.1%
Ovarian disorder	1	0.1%
Endometrial hypertrophy	1	0.1%
Endometrial disorder	1	0.1%
Breast inflammation	1	0.1%
Adnexal torsion	1	0.1%

Source: MO JUMP analysis ADAE3 dataset. SUR. A patient may have had more than one event.

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Analyses by HLT showed that eleven patients had some kind of uterine disorder (including PTs of endometriosis, endometrial disorder, endometrial hypertrophy, adenomyosis, uterine hemorrhage) that was not observed in placebo or in Avonex in the controlled trials, but several of which occurred in studies 201 or 301 on DAC (see Appendix 13.3.3); five patients presented ovarian cysts or ovarian disorder; one had dysfunctional uterine bleeding and two had postmenopausal bleeding. Mean age of the patients was 39 years (median 41; range 22 to 55 years). Mean number of doses received at the time of the SAE was 46 doses (median 47; range 1 to 76 doses). Duration of the event was reported to be approximately one week, except for two cases of endometrial hyperplasia that were reported taking 28 days (201/757-008) and 129 days (303/624-025) to resolve, respectively. Action taken with drug is reported as “none” for 16 of those patients. Patient 201/757-008 was a 22 year old patient diagnosed with endometrial hyperplasia after 4 doses of DAC HYP 300, of mild intensity leading to drug withdrawal.

It is not clear whether daclizumab may have an effect on endometrial function.

- **SAE in Respiratory, Thoracic and Mediastinal Disorders SOC**

There were no SAE in this SOC in study 201. There were more events in the DAC 150 group (6/919, 0.7%) as compared to IFB1a (1/922, 0.1%) in study 301. SAE in 301 are shown below.

Table 32. Patients with SAE in Respiratory, Thoracic and Mediastinal disorders, study 301

	DAC 150 N=919		IFNβ1a N= 922	
	n	%	n	%
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	6	0.7	1	0.1
ASTHMA	1	0.1	0	0
DYSPHONIA	1	0.1	0	0
INTERSTITIAL LUNG DISEASE	1	0.1	0	0
PLEURISY	0	0	1	0.1
PNEUMONIA ASPIRATION	1	0.1	0	0
PULMONARY EMBOLISM	2	0.2	0	0

There are two potentially immune mediated SAEs on DAC 150 (asthma and interstitial lung disease). The listing and selected narratives of patients with SAE in this SOC is included in Appendix 13.3 of this review (13.3.15).

Table 33. Patients with SAE in Respiratory, thoracic and mediastinal Disorders SOC, SUR

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Total DAC experience	DAC HYP N=2236	
	n	%
Patients with any event in this SOC	13	0.6%
Asthma	1	<0.1
Chronic obstructive Pulmonary disease	1	<0.1
Dysphonia	1	<0.1
Idiopathic pulmonary fibrosis	1	<0.1
Interstitial lung disease	2	0.1
Pneumonia aspiration	1	<0.1
Pulmonary embolism	3	0.1
Pulmonary granuloma	1	<0.1
Pulmonary sarcoidosis	1	<0.1
Respiratory failure	1	<0.1

Source: MO analysis. JUMP. SUR ADAE3 dataset.

There were 3 cases of pulmonary embolism (PE) in this application in patients receiving DAC HYP. Deep venous thrombosis (DVT) and PE are not unusual in patients with MS who have limited mobility. One was taking an oral contraceptive, one had Factor V Leiden mutation and a prior history of DVT, and one occurred following surgery on tibia/fibula. Patients had risk factors for the development of DVT/PE and they might have occurred in the absence of daclizumab treatment.

One SAE of aspiration pneumonia is included in this SOC in a patient with worsening MS, described earlier under Infections and Nervous system disorders (303/611-015).

One SAE of pulmonary sarcoidosis is described below.

303/611-029. 25 M received 36 doses of DAC 150 in study 301 and one additional dose in study 303. On Day 16 of study 303 he was hospitalized with recurrent fever for 2 months, edema of the left knee and infiltrative and nodular cutaneous lesions in the thighs. On admission he was found to have an enlarged inguinal lymph node and swelling of the small joints of his hands. On Day 18 of study 303, a computed tomography (CT) scan of the chest showed multiple enlarged hilar and mediastinal lymph nodes. The subcarinal region contained packets of lymph nodes measuring up to 5 cm in diameter. Isolated, micronodular changes were noted in both lungs with areas of streaky fibrosis and pleural thickening. CT findings were consistent with lymphoma or sarcoidosis. Outpatient labs repeatedly showed 15-18% eosinophils (normal up to 6%). During admission he did not have eosinophilia but had elevated CRP, total IgE, ALP and LDH (value not provided). The pathology report of the inguinal node showed a Tcell phenotype consistent with Langerhans cells. There was an elevated number of eosinophils in the T cell zone and isolated macrophages. The finding was consistent with "dermatopathic lymphadenitis." He was treated empirically with antibiotics with no response. In (b) (6) he underwent endobronchial ultrasound-guided transbronchial needle aspiration. The FNA

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showed no suspicious cells; smears contained cellular elements of lymph nodes. IN (b) (6)

he was readmitted to the thoracic surgery department for mediastinoscopy and evaluation of possible sarcoidosis. As per a follow up 15-day safety report samples of the paratracheal lymph nodes showed “chronic non-caseating granulomatous lymphadenitis” consistent with sarcoidosis. Last dose of DAC had been January 2014. As of 28 Jan 2015, the event term was amended to pulmonary sarcoidosis and considered related to the study drug. Treatment included methylprednisolone and prednisone. As per 10/10/15 fu the case is still not resolved.

This patient had a typical presentation for sarcoidosis with bilateral hilar lymphadenopathy and pulmonary micronodules along with joint swelling and skin nodules consistent with erythema nodosum (Lofgren’s syndrome). However, the definitive diagnosis required mediastinoscopy which underscores that FNA and lymph node biopsy of peripheral lymphadenopathy may miss the diagnosis. This case of sarcoidosis is likely related to DAC, and had an onset in study 301, although diagnosis was made in study 303.

Other SAE in this SOC are summarized as follows, and presented in more detail in Appendix 13.3.15 of this review.

- 203/563-001 had recurrent alveolitis and idiopathic pulmonary fibrosis (cryptogenic fibro sing alveolitis with obliterate arteriopathy).
- 301/457-001 (interstitial lung disease) may have had atypical pneumonia that was resolving at the time of the last visit.
- 203/751-015 (interstitial lung disease) had “bilateral interstitial pneumonia” that resolved with sequela after antibiotic treatment.
- 301/554-001 had an event coded as pulmonary granuloma but had miliary lung nodules and mediastinal lymphadenopathy.

Additionally, patient 303/609-013 had interstitial pulmonary nodules and hilar lymphadenopathy. The lung findings were described in the narrative but were not included as AE in the datasets. The patient was suspected of having Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS). The clinical picture is consistent with *sarcoidosis*.

And patient 302/622-502 had interstitial lung disease along with cutaneous nodules that showed non-caseating granulomas and hilar lymphadenopathy. Therefore, this patient also had sarcoidosis.*

Therefore, there are at least 7 SAE consistent with immune mediated lung disease (3 of them with a diagnosis of sarcoidosis or consistent with sarcoidosis). (This does not account for the cases of sarcoidosis reported in January 28, 2016, or the 3 cases of atypical pneumonia mentioned under Infections.)

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Of the cases reported as resolved, by the time they resolved they had received one or more courses of antibiotics and had been off DAC HYP for a several months. On September 28, 2015, DNP asked the applicant to submit additional information about these patients, in particular if there was any additional information about work up done to rule out an immune mediated disease such as sarcoidosis, granulomatous angeitis, eosinophilic pneumonia, but the response added very limited information to what was already in the narratives.

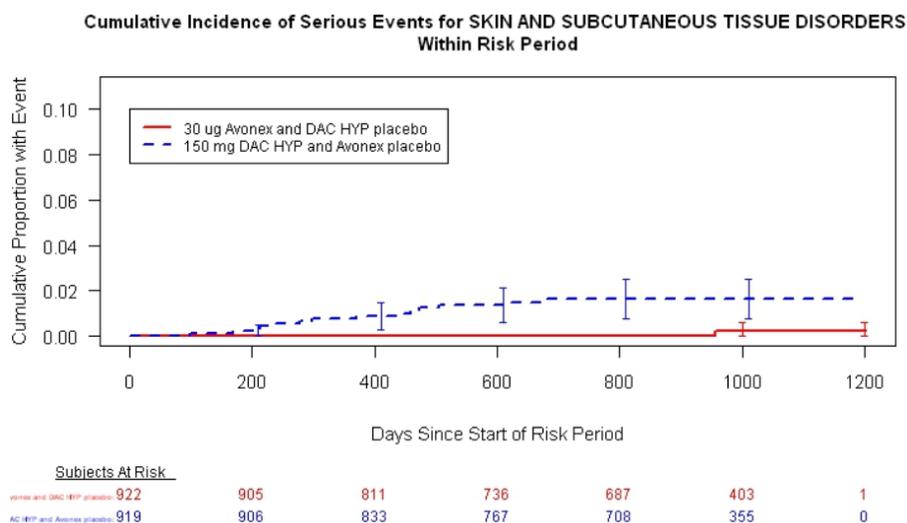
Because of the immunologic effects of DAC HYP on T cell subpopulations, I believe that DAC HYP is inducing or unmasking immune mediated diseases, including sarcoidosis and other lung diseases. For additional discussion see Section 8.5.3 of this review.

- **Patients with SAE in the Skin and Subcutaneous tissue disorders SOC**

In study 201 there were 2 and 3 SAE in this SOC, in the DAC 150 (one rash, one dermatitis exfoliative) and DAC 300 groups (dermatitis allergic, dermatitis atopic and erythema nodosum) respectively. There were no such events in the placebo treatment group. Two of these five reactions occurred during treatment and led to drug discontinuation, and three started as non-serious events during the treatment period and worsened after the drug had already being stopped.

In study 301 there was a clear excess of SAE in this SOC between DAC HYP 150 (n=14, 1.5%) and I IFNβ1a (n=1, 0.1%). The SAE in the DAC 150 group included two cases of angioedema, on of Leukocytoclastic vasculitis, one DRESS, two of psoriasis and one toxic skin eruption. The SAE in the IFNβ1a group was a dermal cyst. As seen in the figure below, the risk of a SAE in this SOC is not immediate; it increases after 200 days (6-7 months.)

Figure 2. Cumulative Serious skin reactions in 301.



Source: Empirica Study. Study 301. Run by Dr. Villalba, July 9, 2015.

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Reviewer Comment: The controlled studies show an excess of serious skin reactions with DAC HYP as compared to placebo or IFNβ1a. There is a suggestion of a dose response between DAC 150 and DAC 300 in study 201 but the numbers are small and the difference is not statistically significant. The overall risk of a serious skin or subcutaneous tissue reaction in the Total DAC HYP experience was 2%.

A summary of SAE in the Skin and Subcutaneous tissue disorders SOC, by MedDRA HLT, Total DAC HYP experience is presented in the following table.

Table 34. Patients with SAE in the Skin and Subcutaneous tissue disorders SOC, by MedDRA HLT, Total DAC experience

HIGH LEVEL TERM/ PT	Total DAC HYP N= 2236	
	n=	%
Patients with any SAE in this SOC	44	2 %
ANGIOEDEMAS Angioedema (2)	2	0.1%
APOCRINE AND ECCRINE GLAND DISORDERS Hydradenitis	1	<0.0%
BULLOUS CONDITIONS SJS (1) Erythema multiforme (1)	2	0.1%
DERMATITIS AND ECZEMA Eczema (3) Dermatitis allergic (2) (LLT <i>toxo-allergic exanthema, toxo allergic dermatitis</i>) Dermatitis atopic (1) (LLT <i>exacerbation of atopic skin Inflammation</i>) Dermatitis (3) (LLT <i>toxic dermatitis; interface dermatitis; Dermatitis</i>)	9	0.4%
DERMATITIS ASCRIBED TO SPECIFIC AGENT Drug eruption (3) (1 attributed to APAP) Toxic skin eruption (3) (LLT <i>toxidermia (n=2); toxicoderma</i>) DRESS (2)	8	0.4%
EXFOLIATIVE CONDITIONS Dermatitis exfoliative (2) (LLT <i>Exfoliative erythroderma; Erythroderma</i>)	2	0.1%
PAPULOSQUAMOUS CONDITIONS Pityriasis rubra pilaris	2	0.1%
HYPERKERATOSES Lichenoid keratosis	1	<0.1%

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PANNICULITIDES Erythema nodosum (3) (<i>LLT Panniculitis nodosa subacute migrans; erythema nodosum (n=2)</i>)	3	0.1%
PHOTOSENSITIVITY AND PHOTODERMATOSIS CONDITIONS Photodermatosis	1	<0.1%
PSORIATIC CONDITIONS Psoriasis (3) Pustular psoriasis (1) (<i>LLT pustules in palms and soles</i>) Erythrodermic psoriasis (2)	5	0.2%
RASHES, ERUPTIONS AND EXANTHEMS NEC Rash (2); Rash maculo-papular (2); Rash generalized (1)	5	0.2%
SKIN INJURIES AND MECHANICAL DERMATOSES Decubitus ulcer	1	<0.1%
SKIN VASCULITIDES Leukocytoclastic vasculitis	1	<0.1%
URTICARIAS Urticaria	3	0.1%

Source: MO JUMP analysis, ADAE3 datasets submitted with SUR.

Overall, they were 30 F, 14 M, ages 19 to 55 years (mean 39 years). Onset was reported from Days 74 to 2004 (mean 510 days). Twenty-three are reported as severe. Five are reported as not resolved. 4 are said to have led to drug withdrawal. At least 15 (0.7%) received treatment with systemic corticosteroids and 5 underwent plasmapheresis. At least 10 had a skin biopsy. Two SAE of were reported after the cutoff of the SUR (302-659-116* cutaneous sarcoidosis and 203/453-014*, parapsoriasis – a premalignant condition-). Selected narratives are shown below. One SAE of angioedema is described under Immune system disorders SOC (*secondary pathway for the angioedema PT*). Listing and additional narratives of SAE in the Skin and SC tissues disorders SOC are included in Appendix 13 (13.3.16) of this review.

301/152-004. **Exfoliative dermatitis and widespread psoriasis.** 43M. A non-SAE of interface dermatitis was reported on Day 362 after 13 doses of DAC (b) (6). Most recent dose had been on Day 337. Prior to this event the patient had an injection site rash at the site of DAC injection followed by a ball-size lesion on the arm and hives on his face. By Day 362 he had diffuse rash in all his body including hands and feet, treated in the emergency room with corticosteroids. On Day 367 he had chills and erythematous, very dry, fissured and crusted patches confluent over a greater part of the face and scalp, particularly the nose and cheeks and scattered erythematous and edematous papules and plaques over the body with few deep seated vesicles on the palms and soles. As per the dermatology report the patient had a history of hand eczema and psoriasis. Treatment included methylprednisolone, antibiotics and prednisone. This “non-SAE” “resolved” on Day 371. However, the same day he was hospitalized with serious AE of worsening interface dermatitis. He had pedal edema and confluent erythema in the face, back, and arm, with a papular erythematous rash on his arms and legs involving palms and soles and psoriatic plaques on his knees and elbows. He had

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peeling skin on several areas along his ears and palms. A skin biopsy was consistent with drug hypersensitivity reaction. DAC was permanently discontinued. He was discharged (b) (6). On Nov 26 he completed the prednisone taper and noted that skin improved until he got down to 10 mg/day. At that time skin eruptions became more erythematous, tender and pruritic requiring going back on prednisone 30 mg/day. On 14 January 2013, the Investigator stated that the subject continued to have a fairly severe, itchy, sore, red, exfoliating rash on the trunk, head, and legs, with lower extremity edema diagnosed as exfoliative erythroderma/widespread psoriasis secondary to hypersensitivity reaction. Furosemide was given for lower extremity edema. He was withdrawn from the study. Last dose had been on Day 337. The final assessment was on Day 701. At the time of the last assessment he had not fully recovered, and it is unclear what the prednisone dose was at that time.

301/512-002, 27 F. Toxic dermatitis. Onset Day 171. No allergies. On (b) (6) (Day 116) a non-serious AE of dermatitis was reported characterized by pruritus and maculopapular exanthema over the head and under the hair later extended to hands and feet. She had received 4 doses of DAC HYP. Most recent dose was on Day 86. On (b) (6) she went to the ER with worsening symptoms and was treated with adrenaline and 2 courses of high dose betamethasone with tapering. On April 12 she had diffuse exanthemas on the trunk and some vesicles on feet, and she was **barely able to her to walk on her feet**. On (b) (6) a skin biopsy was read as “superficial variegated dermatitis featuring eosinophils, though primarily neutrophils, in association with the capillaritis and purpura.” “A complex inflammatory picture suggesting either infectious genesis or drug-induced changes.” Treated with topical corticosteroids and antibiotics. Corticosteroids were stopped by mid-May. An end date for the event of dermatitis was reported on Day 170. However, on (b) (6) (Day 171) she was hospitalized with SAE of toxic dermatitis. At that time she had “widespread eczematous changes on her hands and feet and a toxic dermatitis on the rest of the body. On examination, erythema with swelling, hyperkeratosis, and fissures on the palms of the hands and soles of the feet were observed. Reddened skin changes were seen spread across the torso, buttocks, and the extremities. Some hyperpigmentation in the axillae was observed. Severe scaling of the scalp and less severe peeling around the eyebrows and cheeks were also seen.” Dermatological manifestations started to improve after 3 plasmapheresis treatments. The event of toxic dermatitis was reported related to study drug and improved as of (b) (6) (Day 180). At that time there was no skin rash but there was mild hyperkeratosis on the palms and soles and scaling of the scalp. The event was completely resolved on (b) (6) (Day 331), almost 9 months after discontinuation of daclizumab.

Three cases of DRESS were identified in this application (two reported by the investigators, and one reported as Stevens-Johnson syndrome that upon review is consistent with DRESS). These cases are discussed in Section 8.5.3. Immune mediated reactions.

Additional narratives of SAE in the Skin and SC SOC are included in Appendix 13.3.16 of this review.

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DAC HYP is associated with serious skin reactions in 2% of patients exposed. Clinical distinction between various reactions is difficult. For additional discussion see Section 8.5.2 of this review (Specific safety issues)

- **SAE in the Surgical and Medical Procedures SOC.**

There were no SAE in this SOC in study 201. There were more events on DAC HYP than IFNβ1a in 301, but the type of procedures was heterogeneous. SAE in this SOC in the Total DAC included spinal decompression, angioplasty, rehabilitation therapy, mammoplasty, eyelid surgery, abortion induced, hysterectomy and drug detoxification. None led to drug discontinuation.

Reviewer Comment: Medical and surgical procedures done in the context of the evaluation of adverse events that developed during treatment with DAC HYP were not systematically collected in this database. Based on review of individual narratives at least 8 patients underwent liver biopsy; at least 12 patients underwent colonoscopy and biopsy for work up of colitis related terms; at least two underwent thoracoscopy and lung biopsy; others underwent transbronchial lung biopsy; two had kidney biopsies. Several underwent lymphadenectomy (mostly cervical, axillary or inguinal) but some underwent transbronchial biopsy of hilar/mediastinal adenopathy. At least 5 underwent plasmapheresis. At least 4 underwent blood transfusions. Several patients are likely to have been intubated (e.g. while in the ICU with suspected sepsis), at least one had a tracheostomy, but that information was not adequately captured.

These are invasive procedures with associated morbidity that are likely to interfere with the quality of life of these patients and may undermine any potential beneficial effect of DAC HYP in reducing the rate of MS relapse. Some of these procedures were included in the concomitant medications datasets (non-drug treatment category), but not all of them are there. We could ask the applicant to search their database and create a dataset with procedures that patients had to undergo in these clinical trials.

- **SAE in the Vascular Disorders SOC**

There were few events in this SOC in the controlled trials. In 201 there was one event of circulatory collapse (same patient with hypersensitivity after 1 dose of DAC 300).

In 301 there were four SAE on DAC HYP 150 (one circulatory collapse, one hypotension and two cases of vasculitis (one Kawasaki's disease and one of cutaneous vasculitis); and one SAE on IFNβ1a (venous thrombosis). A few additional SAE were reported in this SOC in the Total DAC experience (2 deep venous thrombosis, one hypertension, one hypotension, one varicous vein). The case of "circulatory collapse" (201/752-210 was discussed along with acute hypersensitivity reactions) and the case of systemic vasculitis (301/606-020, MPO-ANCA positive Kawasaki syndrome) was discussed under Infections. A SAE of cutaneous vasculitis is included below.

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301/660-008. CUTANEOUS VASCULITIS. 37 F on DAC 150 developed non-SAE of “vasculitis” on Day 245, which became serious on Day 254, listed as resolved on Day 277. DAC was interrupted. The only concomitant med at the time listed in profile is was paracetamol. As per the hospital discharge summary the patient had hypothyroidism and arterial hypertension, treated with thyroxin and Ramipril, respectively. Local labs were negative for “a number of autoantibodies”. She was admitted to hospital due to vasculitic exanthema of the lower and upper limbs. A biopsy of the forearm showed leukocytoclastic vasculitis. She was treated with IV MP, prednisone 40 mg/day and betamethasone and other topical treatments, and clarithromycin, and was discharged on prednisone 20 mg/day. On last dermatology follow up she was still on prednisone 15 mg/day. She completed 301 and continued into study 303. She later had a SAE of “Erythema multiforme” on Day 905 in study 303. *(This is different from the case of leukocytoclastic vasculitis reported under the Skin disorders SOC) For further discussion see Section 8.5.3 (Specific safety issues).*

Two SAE of DVT were reported in this SOC after 523 and 609 days of DAC treatment (301/110-008 and 202/450-003, respectively). DVT is not unexpected in patients with MS who have limited mobility. They resolved and did not lead to drug discontinuation.

OVERALL CONCLUSION OF SAE SECTION: Evaluation of SAE indicate that DAC HYP is associated with severe immune-mediated reactions involving the liver, skin, GI system and other organs, as well as systemic inflammatory reactions that require invasive diagnostic procedures and additional immunosuppressive therapy. The risk of serious infections is also increased in DAC150 as compared to placebo and IFNβ1a. Malignancies, particularly breast cancer and lymphoma, are of concern with prolonged use of DAC HYP.

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8.4.3 Dropouts and/or Discontinuations Due to Adverse Effects

As described in section 5, the protocols include pre-specified criteria for drug and study discontinuation. Those criteria appear adequate.

*Reviewer Comment: The numbers of AE dropouts in study 201 and 301 generated with Empirica study are slightly different from the analyses presented by the applicant. Separate from the reassignment of the reason for discontinuation, the analyses of dropouts due to AE in this database are not reliable, as discussed in Section 8.1 Quality of the application). I am presenting the analyses of AE leading to drug discontinuation as submitted in the AE datasets but **I do not believe that they accurately reflect whether treatment continued or not.***

There were few events leading to drug discontinuation in 201, however, despite the small size of the trial, there is a higher incidence among patients treated with DAC HYP (3-4% of patients) as compared to placebo (1%), with a suggestion of a dose response between DAC 150 and 300. The most common cause of drug discontinuation was in the Skin and subcutaneous tissue disorders SOC, and involved various preferred terms related to dermatitis, drug eruption, rash, all in the DAC HYP treatment groups. No such cases were reported with placebo.

In study 301, the risk of withdrawal because of an AE was slightly higher on DAC 150 as compared to IFN β 1a (15% vs 12%, respectively). The most common reasons for drug withdrawal were in the Investigations SOC (mostly hepatobiliary investigations) which occurred in 5% and 4% of patients on DAC150 and IFN β 1a groups, respectively (*not very different*). The next most frequent SOC was the Nervous system disorders (1.5% and 3.5 %, respectively, *higher on IFN β 1a than DAC HYP*), followed by the Skin and subcutaneous tissues disorders SOC (1.5% and 0.1%, respectively). AE dropouts occurred throughout the study but separated from IFN β 1a after 500 days.

Summary tables of AE dropouts in studies 201 and 301 by SOC and PT and time to event plots are presented in Appendix 13 of this review (13.3.3).

Dropouts in the Total DAC HYP experience

Based on the SUR datasets, the total number of patients who discontinued because of an AE was 320; excluding patients who dropped because of MS the number was 298. Summary tables of patients who discontinued drug due to adverse events by SOC, are shown below.

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Table 35. Patients with adverse event leading to drug discontinuation, Total DAC HYP database

	All DAC HYP N=2236	
	n	%
Patients with Any event leading to drug WD	320	14.3
Patients with Any event leading to drug WD except MS¹	298	13.3
INVESTIGATIONS	116	5.2
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	88	4.0
NERVOUS SYSTEM DISORDERS (all)	31	1.4
Nervous system disorders except MS ¹	8	0.4
HEPATOBIILIARY DISORDERS	25	1.1
GASTROINTESTINAL DISORDERS	21	0.9
INFECTIONS AND INFESTATIONS	19	0.8
BLOOD AND LYMPHATIC SYSTEM DISORDERS	17	0.7
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS)	9	0.4
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	8	0.3
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	4	0.2
IMMUNE SYSTEM DISORDERS	3	0.1
PSYCHIATRIC DISORDERS	3	0.1
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	3	0.1
RENAL AND URINARY DISORDERS	2	0.1
REPRODUCTIVE SYSTEM AND BREAST DISORDERS	2	0.1
VASCULAR DISORDERS	2	0.1
CARDIAC DISORDERS	1	0.0
ENDOCRINE DISORDERS	1	0.0
PREGNANCY, PUERPERIUM AND PERINATAL CONDITIONS	1	0.0

Source: MO JUMP analysis. ADAE3, SUR. Up to 180 days post dose. ¹ Patients with events except MS/MS relapse calculated from AE datasets using JUMP, by excluding the following preferred terms: multiple sclerosis, multiple sclerosis relapse and progressive multiple sclerosis.

Overall, 14.3% of patients dropped out treatment because of an adverse event. The most common causes of drug discontinuation were in the Investigations, Skin and subcutaneous tissue disorders SOC, the Nervous system and Hepatobiliary SOCs. Most dropouts from the Nervous system SOC were events of MS relapse (1% of patients in MS trials). Dropouts by SOC are discussed below, in alphabetical order.

- **Dropouts due to AE in the Blood and lymphatic system Disorders SOC**

There were no dropouts in this SOC in study 201. In study 301, 8 (0.9%) and 3 (0.3%) patients had an AE that led to drug withdrawal in the DAC150 and IFNβ1a groups, including 5 of lymphadenopathy/lymphadenitis in the DAC HYP 150 group as compared to none on IFNβ1a. AE dropouts in the Total DAC HYP experience are summarized below.

Table 36. AE Dropouts due to Blood and Lymphatic system disorders SOC, Total DAC experience

PT	Total DAC HYP N=2236	
	n	%
Any patient with AE leading to drug withdrawal in this SOC	17	0.7
LYMPHADENOPATHY	13	0.6
LYMPHOPENIA	2	0.1
AGRANULOCYTOSIS	1	<0.1
LYMPHADENITIS	1	<0.1

FDA MO JUMP analysis ADAE3 SUR

As of the SUR, a total of 17 patients discontinued study drug because an AE in this SOC of whom 14 discontinued because of lymphadenopathy/lymphadenitis. Of these cases, 10 were female and 4 were male; time of withdrawal was 957 days (range 150 to 2346 days). Overall, Of the 17 events leading to drug discontinuation 6 were serious and have been discussed in the SAE section. Non-serious AE leading to drug withdrawal in this SOC are listed in Appendix 13 (13.3.7). The issue of lymphadenopathy has been extensively discussed under SAE.

- **AE dropouts in the Cardiac Disorders SOCs**

There were no AE leading to withdrawal from these SOCs in study 201; a 50 year old female discontinued because of non-serious symptomatic bradycardia on Day 757, after 26 doses of DAC 150 (301/129-001). The event is listed as not resolved. There were no additional withdrawals due to AE in this SOC in the Total DAC HYP database.

- **AE dropouts in the Congenital Disorders SOC**

There was one case in study 201, as follows. 201/509-007 had ALT elevation up to 47xULN along with AST, LDH and GGT elevation after 12 doses of DAC HYP 150. On Day 330, **ALT was 1628 U/L (47xULN)** and **AST was 27xULN**, therefore, the last dose (#13, week 48) was not given. On Day 344 she was diagnosed with **hepatic arteriovenous malformation** and did not enter the extension study. Abdominal US and CT of the abdomen showed steatosis and AV malformation. Liver enzymes improved after drug discontinuation. The event was considered

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resolved by Day 403. Liver enzymes were normal by Day 512. Neither the narrative nor the patient profile mentions Hepatitis profile or ANA and autoantibody workup. This patient was anti-DAC antibody negative at weeks 0, 24, and 52; but she was anti-DACab positive at weeks 62 and 72 (titer: 46.6). The patient was not obese. There is no information about hepatitis workup, ANA or other liver specific antibodies or alcohol use.

This case was identified in the RLQ of the ALT by BR plots but was not reported as an AE in the hepatobiliary or investigations SOC. I have mentioned this case among the potential cases of DILI when discussing Hepatobiliary SAE. I believe the arteriovenous malformation was an incidental finding. There was no testing to rule out other etiologies but the normalization of liver enzymes 3 months after stopping DAC is consistent with a DAC HYP induced reaction. This is an example of inappropriate coding and of an apparent “no action taken with drug” when the drug was in fact discontinued because the patient was at the end of 301. The positive anti DAC antibody at the end of the trial is of unclear clinical significance.

- **AE dropouts in the Endocrine Disorders SOC**

There were no AE leading to drug withdrawal in this SOC in study 201; there was one non-serious case of autoimmune thyroiditis in study 301, as follows.

301/624-004 was a 27 year old F who developed autoimmune (Hashimoto) thyroiditis after 7 doses of DAC HYP 150 mg (week 24 of study). Concomitant med during the study was paracetamol. At the time of the diagnosis of thyroiditis (week 24) she had low thyrotropin and ALT/AST elevation. She was treated with levothyroxine. Drug was discontinued. At the early termination visit ALT & AST were 4xULN. The event was reported as not resolved. There is no follow up of ALT values.

There were no other dropouts in this SOC in total DAC experience.

- **AE dropouts in Gastrointestinal Disorders SOC**

There were no dropouts in this SOC in study 201. In study 301 there were 3 events on DAC HYP (one colitis, one ulcerative colitis and one plicated tongue) as compared to 1 on IFNβ1a (flatulence). AE dropouts in the Total DAC HYP experience pool in the GI disorders SOC (n=19) are summarized below.

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Table 37. AE dropouts in the GI Disorders SOC, Total DAC experience

	All DAC HYP N=2236	
	n	%
ANY	19	0.8
Colitis ulcerative	5	0.2
Colitis	4	0.2
Diarrhea	2	0.1
Crohn's disease	1	<0.1
Coeliac disease	1	<0.1
Colitis microscopic	1	<0.1
Lip swelling	1	<0.1
Obstruction gastric	1	<0.1
Edema mouth	1	<0.1
Oral pain	1	<0.1
Pancreatitis	1	<0.1
Plicated tongue	1	<0.1
Proctalgia	1	<0.1

MO JUMP analysis ADAE3, SUR. One patient had three events.

Of the 21 events in 19 patients leading to WD in this SOC, 6 were serious and already discussed under SAE. Some of the non-serious events occurred in patients with other SAE were already discussed (e.g. non-serious diarrhea leading to withdrawal in patient with serious colitis).

Non-SAE leading to withdrawal are listed in Appendix 13.3.9 of this review. They include four cases of inflammatory colitis. Three of them required high dose corticosteroid treatment (ulcerative colitis [202/505-014] on Day 650; Crohn's disease [203/365-002] on Day 1636; colitis, later diagnosed as Crohn's [203/559-002] on Day 832 (also required azathioprine). They were ongoing at the time of the SUR, receiving an unknown dose of CS/azathioprine. The fourth had a diagnosis of microscopic colitis [303/165-002] on Day 1160 treated with budesonide and reported as resolved, although it is unclear for how long the patient required treatment. Of the patients with Crohn's disease, one was associated with "panarteritis nodulosa benigna" and the other with ALT >5x ULN at the time of the event. Of the four cases of colitis, three had weight losses of 4 to 12 kg over the 2-3 year period but one patient with Crohn's increased 30 kg between baseline in study 301 to end of study in 303 (perhaps related to extensive use of high dose steroids). One patient with recurrent diarrhea but no diagnosis of colitis also had weight loss (10 kg over 2 year period). The cases of UC and Crohn's and the angioedema like event occurred in patients who had received DAC300 in study 201, but were receiving DAC150 at the time of the event.

203/306-001) had lip swelling, mouth edema and oral pain after 86 doses of DAC

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She also had face swelling, generalized eczematous dermatitis and lymphadenopathy, consistent with an allergic reaction that is difficult to classify (angioedema like reaction on top of chronic dermatitis). *There is limited information to determine if this is DRESS.*

One case of pancreatitis (202/758-016) was withdrawn after 16 doses of DAC150. There is limited information about this patient.

Comment: Even though “non-serious” most patients with diagnosis of colitis/UC/Crohn’s underwent diagnostic colonoscopy; some required treatment with corticosteroids and or azathioprine. Several of these events were not resolved at the time of the last follow up. Some patients presented notable weight loss; however, one patient gained almost 30 pounds, perhaps because of the prolonged use of corticosteroids. For additional discussion see Section 8.5.3 of this review.

- **AE dropouts in the General Disorders and Administration site conditions SOC**

There were no AE dropouts in this SOC in study 201. In study 301, 7 patients on DAC150 discontinued drug because of adverse events (1 multiorgan failure, 1 gait disturbance, 1 local swelling and 3 injection site reactions and one influenza like illness) as compared to 11 patients on IFN (7 influenza-like illness, 1 injection site reaction, 1 pyrexia, 1 facial edema and 1 asthenia). One more patient discontinued from study 203 (203/561-002, drug withdrawal syndrome, unrelated to DAC).

As per the AED3 datasets, of the 8, two were serious (multiorgan failure discussed under SAE and injection site reaction, described below) and 6 were non serious. Of 6 non-serious events, two had not resolved at the time of last follow up. These were the event of gait disturbance (301/145-004, reported by the investigator as “accrued disability walking”) occurred in a patient who had two prior episodes of MS relapse) and likely represented lack of efficacy and the case of flu-like illness (301-475-003, no other AE reported at the time of this event). Local swelling of lips and hands was consistent with angioedema and reviewed under the Skin and SC disorders SOC. Three patients with AE of injection site reaction as follows: 301/554-011, injection site erythema on Day 13, after 1 dose of DAC, leading to drug withdrawal. There is no end date for this event. She had fever for 2 days prior to the local reaction.

301/325-004 had SAE of injection site erythema on Day 198 after 8 doses of DAC HYP that lasted 11 days. She had had injection site erythema after dose #1, injection site pruritus after dose #6 and injection site macula after dose #7. On Day 224 she presented rash on face and upper chest that resolve after 2 days. 301/178-001 had pain at the injection site, on Day 340, after 14 doses of DAC that resolved after 44 days. No other events reported at that time.

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- **AE dropouts in Hepatobiliary Disorders SOC and Investigations (Hepatobiliary HLGT)**

Table 38. Patients with AE leading to drug withdrawal in Hepatobiliary SOC and Investigations SOC/Hepatobiliary HLGT, controlled trials

Study 201			Study 301	
DAC150	DAC300	Placebo	DAC150	IFNβ1a
N=207	N=208	N=204	N=919	N=922
3 (1.4)	1 (0.5)	1 (0.5)	49 (5.3)	36 (3.9)

In study 201 only one patient had one event leading to drug withdrawal in the Hepatobiliary SOC (on DAC300) and three in the Investigations SOC (Hepatobiliary HLGT) as compared to 1 on placebo (cholelithiasis). In study 301, 49 (5.3%) and 36 (3.9%) patients had AE that led to drug withdrawal in these SOCs in the DAC 150 and IFNβ1a groups respectively. The mean number of days to onset of the event leading to drug withdrawal was 507 (median 513, range 59-953) on DAC150 and 305 (median 197, range 25-929) for IFNβ1a. The number of DAC150 doses taken before drug withdrawal was 18 (median 17, range 3 to 35 doses). *Withdrawal related to liver events occurred later with DAC150 as compared to IFNβ1a and most occurred after the first year of treatment.* A summary table of AE leading to withdrawal in the Total DAC experience, by HLGT is shown below.

Table 39. AE leading to drug withdrawal in Hepatobiliary and Investigations (Hepatobiliary HLGT) SOCs, Total DAC HYP experience.

	N= 2236	
	n	%
Subjects with ANY AE	112	5.0
ALT increased	38	1.7%
Liver function test abnormal	28	1.3%
AST increased	19	0.8%
Hepatic enzyme increased	14	0.6%
Hepatitis, hepatitis toxic, hepatitis acute, Hepatotoxicity, drug induced liver injury	8	0.4%
Blood bilirubin increased, hyper BR	8	0.4%
GGT increased	4	0.2%
Liver disorder	4	0.2%
Autoimmune hepatitis	3	0.1%
Jaundice, jaundice hepatocellular, acute hepatic failure	4	0.2%
Biliary colic, cholelithiasis, cholecystitis chronic	3	0.13%
Hepatic lesion	1	0.04%
Alcoholic liver disease	1	0.04%

FDA MO analysis, JUMP ADAE3 datasets submitted with SUR. One patient may have more than one event. Includes terms as presented in the ISS as of the SUR (three cases of autoimmune hepatitis were coded under other liver related terms.)

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Overall, 144 patients discontinued drug because of hepatobiliary disorders or investigations in the total DAC database. All SAEs led to drug withdrawal and were already reviewed in the SAE section of this review. Of the Investigations (Hepatobiliary HLGT) leading to withdrawal, the great majority were non-serious. (Of note, per protocol, patients with ALT or AST >5xULN had to be withdrawn from the study.) A listing of patients with AE dropouts that were “non-serious” but led to drug discontinuation (N=99 subjects) is included in Appendix 13 of this review (generated from FDA medical officer from ADAE3 submitted with the SUR) (13.3.4). Review of these cases showed that most were just above the 3 to 5x ULN, but several cases had substantially high ALT values (>15-20x ULN, mostly with normal BR values).

As per review of the narratives, at least 30 of the non-SAE that led to drug withdrawal in the hepatobiliary and investigations SOCs were confounded by use of potentially hepatotoxic medications including IV MP, analgesics (NSAIDs, APAP, tramadol), amoxicillin, nitrofurantoin, antidepressants, muscle relaxants, antiepileptic drugs or alcohol. Some were confounded by possible infections (Hepatitis E, VZV, HVS, CMV, Hep B). Some of them occurred in patients who had also developed some kind of rash (maculopapular, exanthematous, dermatitis, psoriasis), lymphadenopathy (at least 3) and one occurred in a patient who had received a diagnosis of Crohn’s disease. None of them was treated with high dose long term corticosteroids although some received short courses of systemic corticosteroids for concomitant rash (301/228-003) or polyarthritis (203/769-005). At least 11 were not resolved at the time of the SUR.

Selected cases of non-SAE leading to drug withdrawal are included below.

301/205-006 was a 31 yo F with Hx of hypothyroidism. Concomitant meds included levothyroxine and oral contraceptive. She had ALT>3xULN on Day 420 after 16 doses of DAC. Drug was interrupted, APAP and DAC HYP were stopped and enzymes normalized by Day 466. DAC re-started, ALT increased again by Day 527. Last dose of DAC was on Day 561. ALT peaked at 50x ULN on Day 583; AST 20x ULN, BR was 1.5xULN (but 10 fold from baseline) Direct BR was 2xULN. ANA was + 1:80; IgE was high. AMA/ASMA were negative; LKM-1 was 5.4. On Day 696 developed allergic dermatitis, treated with oral corticosteroids (unknown dose) for 2 weeks. IFNβ1a started on Day 733. Liver enzymes slowly improved and were normal by Day 1002. *In my opinion this case is consistent with DILI; as per Dr. Avigan’s evaluation, the case is of “probable/possible” relatedness to DAC. She had a positive ANA (1:80); liver auto ABs were considered negative. Dr. Avigan speculates that the patient had **underlying AIH** that was aggravated because of treatment with DAC HYP. Interestingly, laboratory values improved while the patient was on IFNβ1a.*

301/541-005, 26 M was diagnosed with a non-SAE of hepatitis toxic (AE TERM “**cryptogenic hepatitis**” probably toxic). There is no description about the work up. He had modest ALT elevation that peaked at 3xULN on Day 913, 43 days after the last dose of DAC150 and normal

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BR. It is unclear how this diagnosis was made. Event was preceded by toxico-allergic dermatitis that started on Day 725. He was treated with URSO and there is no mention of corticosteroids. The event was reported as resolved on Day 1067 almost 6 months after the last dose of DAC, however, he was withdrawn from the study and there is no further follow up. *In my opinion this is immune mediated hepatitis.*

301/451-005. 54 F. PT: Abnormal liver enzymes. Patient underwent angioplasty procedure on (b) (6) (Day 77) (after 3 doses of DAC HYP) and started clopidogrel and aspirin treatment. ALT & AST started to increase on (b) (6) (Day 92). An event of liver function abnormal was reported on Day 174 (the day of dose #7), leading to drug withdrawal. ALT peaked at 7x ULN on Day 189 and normalized on Day 268, 6 months after the last dose of DAC HYP. An AE of **pustular psoriasis** was reported on day 156, not resolved. Labs showed **eosinophilia** (6.9%) on Day 268, at the last visit, and there is no follow up. Urine showed intermittent trace protein. Liver autoABs negative. DAC ab neg. Not resolved as of the SUR. *There was ALT elevation with concurrent pustular psoriasis and eosinophilia. ALT elevation resolved 6 months after drug discontinuation but pustular psoriasis and eosinophilia did not. In my opinion this is consistent with **immune mediated hepatitis**.*

One case consistent with Primary Biliary Cirrhosis (PBC) was identified among the dropouts in this database:

302/622-108: 51 F. The patient had mild ALT & AST elevation at baseline, but on the day of the 4th dose of DAC150 (Day 88) had ALT 3.6xULN, with mild AST elevation (normal BR, GGT and ALP). No further doses were given. As per the patient complained of arthralgia since Day 57. ALT peaked one month later (ALT >5 but <10x ULN) with mild increase in AST/GGT and ALP. ALT resolved by Day 157 but ALP started to increase on Day 184 (almost 3 months after last dose of DAC), with peak around Day 282, along with GGT elevation. Cholelithiasis was reported on Day 253. Patient was treated with IFNβ1a for about 2 months starting on Day 193 but stopped because of flu-like symptoms. Events were not resolved as of Day 334 of the study. As per review of the listing of antibody testing conducted in the trials submitted in May 2015, this patient had a positive Anti-mitochondrial Ab (typically associated with PBC) on Day 113. *This patient may have had underlying PBC that was exacerbated by DAC HYP use. Unfortunately there is relatively short follow up to evaluate whether event fully resolved or not.*

Given the limitations of the AE datasets described under Quality of the application, analyses of duration of events, action taken with drug and outcome are not helpful in this database. In fact, MO analyses in the ISS showed that of the 90 patients listed as leading to drug interruption in the Hepatobiliary and Investigations SOCs, 13 (14%) actually discontinued drug because of an adverse event on that date or close to that date (11 because of a liver related AE and four because of another event: 1 colitis, 1 eczema, 1 macular rash and 1 MS relapse.) Those patients are listed in Appendix 13.3.3 of this review after the listing of AE leading to drug withdrawal.

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Those who discontinued because of some other liver event are included among the cases listed in Table 35. The patients who discontinued for reasons other than liver AE are not.

Additional potential case of DILI

201/903-025. 31 M presented elevated ALT/AST and GGT after 7 doses (week 24) in the DAC 150 mg group. At that visit **ALT was 28x ULN**, AST was 11 xULN and GGTP was 2xULN. Values prior to week 24 were normal, and returned to normal by week 28. Total BR was always normal. He received 4 more doses without increase in liver enzymes. However, the patient was terminated from the study because the sponsor closed the site upon learning that the pharmacist was purposefully giving the wrong medication. It is unknown whether the patient received DAC 150 or DAC 300. *Ideally, the patient should have been followed for at least 180 days.*

- **AE dropouts in Metabolism and nutrition disorders SOC**

As per the SUR AE datasets, no event led to drug discontinuation from this SOC.

- **AE Dropouts in Immune system disorders SOC**

Only three AEs are listed as leading to drug withdrawal WD in the Immune system disorders in the DAC HYP database. One was serious and described under SAE (“Hypersensitivity” in patient 201/752-010). The other two are non-serious AEs of **sarcoidosis**, as follows.

301/659-014- 41 year old M was diagnosed with sarcoidosis after 28 doses of DAC HYP 150 mg. The event was not resolved at the time of last follow up.

303/659-001 – 26 year old F diagnosed with sarcoidosis after 39 doses of DAC HYP 150. Not resolved at time of last follow up.

There was very limited data about these cases of sarcoidosis. The FDA requested additional information about these cases but nothing substantial was added.

A non-SAE of presyncope as “presyncope” associated with palpitations and weakness, followed by skin rash the day after the first dose of DAC300 (201/458-007) consistent with acute hypersensitivity was reported under the Nervous system disorder SOC and should be analyzed along with other such cases.

For additional discussion about Immune mediated disorders see Section 8.5.3 of this review.

- **AE dropouts due to Infections and Infestations SOC**

The percentage of infections leading to drug discontinuation in the controlled trials was small. In 201 two events led to drug withdrawal in this SOC (201/763-005, hepatitis B and 201/763-005, yersinia infection). Both SAE were already discussed. In 301, 0.5% patients discontinued because of an AE in this SOC in the DAC HY 150 group as compared to 0.3% on INF. Overall, 18

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patients (0.8%) discontinued drug because of an infection in the Total DAC HYP database. Of those, 11 were serious (discussed under SAE) and 7 were not. Of the 18, 6 were reported as not resolved at the time of the SUR. Patients with events leading to drug withdrawal are summarized below, followed by the listing of the non-serious events.

Table 40. AE dropouts in the Infections and Infestations disorders SOC, Total DAC HYP

	All DAC HYP N= 2236	
	n	%
Any patient	18	0.8%
Pneumonia	3	0.1%
Pulmonary tuberculosis	3	0.1%
Urinary tract infection	2	0.1%
Yersinia infection	1	<0.1%
Atypical pneumonia	1	<0.1%
Brucellosis	1	<0.1%
Chronic hepatitis b	1	<0.1%
Epstein-Barr virus infection	1	<0.1%
Hepatitis viral	1	<0.1%
Infectious mononucleosis	1	<0.1%
Meningitis aseptic	1	<0.1%
Pharyngitis	1	<0.1%
Tuberculosis	1	<0.1%

MO analysis, ADAE3 SUR

Overall, the most common cause of drug discontinuation in this SOC was tuberculosis (n=4) and pneumonia (n=4). As of the cutoff of the SUR, four cases of tuberculosis had led to drug withdrawal, including 3 pulmonary TB (including one serious [301/611-009]). Of note, three of these cases were categorized as “non serious” because the patients were not hospitalized although I would think that a case of tuberculosis is an important medical event, regardless of whether it causes hospitalization or not.

There were also 4 withdrawals because of pneumonia (including one atypical pneumonia). After the cut-off of the analyses of the SUR, there was one report of pneumonia “possible tuberculosis” described under SAEs. Additionally, the patient with diagnosis of brucellosis was treated empirically with anti-TB therapy.

There are at least 5 cases of TB in this application. Serious cases leading to drug discontinuation were already discussed. The cases that were reported as non-serious are included below along with other infections leading to WD.

Patients with non-serious AE leading to drug withdrawal in Infection and Infestations SOC

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201/763-005	24 F chronic hepatitis b of moderate intensity on Day 221, withdrawn after 9 doses of 150 mg DAC HYP. Reported as not resolved.
301/476-009	44 M. Pharyngitis of moderate intensity started on Day 97, withdrawn after 4 doses of 150 mg DAC HYP
301/743-001	41 F from India. Tuberculosis diagnosed after 34 doses of 150 mg DAC HYP. She first presented a SAE of left submandibular swelling (lymphadenopathy) diagnosed as lymphoid tissue hyperplasia by fine needle aspiration. It is reported to have “resolved” with cephalosporin treatment 3 days after diagnosis. Then, on Day 936 she had a “non-serious” event of tuberculosis that led to drug withdrawal. Diagnosis was made by another FNA (location not specified). Last dose of DAC was on Day 925. She was treated with ethambutol, isoniazid, pyrazinamide and rifampicin. The event resolved after 41 days (Day 976).
203/761-007	37 M. Epstein-Barr virus infection, reported as “activation phase”, of mild intensity on Day 1346 after 37 doses of 300 mg DAC HYP Reported as not resolved. (<i>“Analysis not done” as per September 2015 response</i>)
203/909-008	45 F. from Ukraine. Pulmonary tuberculosis of severe intensity was reported on Day 939, after 33 doses of 150 mg DAC HYP. At that time WBC had was within normal, with normal differential. Drug was withdrawn. No further details were given on diagnostic testing. Reported as not resolved as of the SUR.
303/537-014	34 M from Russia. As per datasets, Pulmonary tuberculosis of moderate intensity was reported on Day 813, after 28 doses of 150 mg DAC HYP. Reported as not resolved.

There is little information in the narratives about these patients in terms of symptoms, WBC values or how the diagnosis was made. If drug is approved, ppd testing should be recommended.

- **AE dropouts Neoplasms benign, malignant and unspecified (incl cysts and polyps) SOC**

There was no excess of neoplasms leading to drug withdrawal in the DAC HYP treatment group as compared to placebo or IFN in the controlled studies. Overall, nine patients had neoplasms leading to drug withdrawal in this SOC in the Total DAC HYP database. They were 4 breast cancers, one ovarian cancer, one uterine cancer, one brain cancer, one prolactinoma, one uterine leiomyoma. They were all serious and discussed previously under SAE.

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- **AE dropouts in Nervous system SOC**

A total of 31 patients discontinued drug treatment because of AE in the total DAC HYP database. Of those, 23 were MS or MS relapse. Of the patients who dropped drug treatment because of AE in this SOC excluding MS relapse (n=8) 4 were serious (syncope, brain edema, myasthenia gravis, status epilepticus, reviewed under SAEs) and 4 were not. The non-serious events leading to withdrawal in this SOC were headache (301/139-001, and 303/128-006, of moderate intensity, one after 3 doses of DAC and one after 1 dose of DAC; both recovered after approximately 2 months), polyneuropathy (302/659-103 of severe intensity after 13 doses of DAC HYP, had not resolved as of the SUR) and presyncope (201/458-007). A summary of AE leading to dropout in the controlled trials is shown below.

Table 41. Dropouts because of Nervous system disorders AE other than MS are summarized below.

Study 201			Study 301	
DAC150	DAC300	Placebo	DAC150	IFNb1a
N=207	N=208	N=204	N=919	N=922
n %	n %	n %	n %	n %
0	2 (1)	0	2 (0.2)	3 (0.3)

One event of interest, related to hypersensitivity was coded under this SOC. The narrative is as follows.

201/458-007, 46 F presented presyncope of moderate intensity on Day 30. Withdrawn after 2 doses of DAC HYP 300. She presented presyncope along with sweating, weakness, palpitations the day after the second dose; and rash, one day later. The rash was treated with betamethasone and levocetirizine. *Event reported as resolved after 17 days. Rash resolved 2 months after drug discontinuation. This is an allergic reaction to DAC HYP.*

- **AE Dropouts Musculoskeletal and connective tissue Disorders SOC**

There were no imbalances in the controlled studies. As per the AE datasets there were only 4 events leading to drug withdrawal in the DAC HYP database. Of those, one was serious and already discussed under SAEs (Lupus-like syndrome), and three were non-serious and moderate in intensity.

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Table 42. AE Dropouts in Musculoskeletal and Connective tissue disorders

Table 14.a, Study 201 SOC/PT	Total DAC HYP N=2236	
	n	%
Patients with any event in SOC	4	0.2
Arthritis	1	<0.1
Arthralgia	1	<0.1
Lupus-like syndrome	1	<0.1
Seronegative arthritis	1	<0.1

ADAE3.

Patients who withdrew drug because of AE in this SOC were 2 female, 2 male, ages 25 to 50 years. Mean time to onset of event leading to drug withdrawal in this SOC was 514 days (median 599, range 69 to 791). Patients received a mean of 18 doses (median 21, range 3 to 28). The case of lupus-like syndrome was already discussed under SAEs.

The narratives of the non-SAE leading to drug withdrawal contain very limited information to assess whether the cases are truly inflammatory or if arthritis (lack of X-ray reports, markers of inflammation such as CRP and ESR, or antibody panels). Narratives of these patients are included in Appendix 13.3.9, after the listings of Infections.

- **AE dropouts in Pregnancy, puerperium and perinatal conditions SOC**

As per the datasets, one patient discontinued DAC HYP because of an AE in this SOC. It was a 24 year old female who had a spontaneous abortion on Day 607, after 20 doses of DAC HYP (202/110-006). Two additional patients discontinued treatment after a spontaneous abortion (discussed under SAE).

- **AE dropouts in the Psychiatric Disorders SOC**

Three patients dropped out because of an AE in this SOC. There was one event of suicidal ideation (serious, in 301 on Day 360) and two non-SAE of worsening depression (Day 1127) and one of anxiety (Day 100). They are reported as resolved after a few days to 1 month later.

- **AE dropouts in Renal and Urinary Disorders SOC**

Two patients discontinued because of events in this SOC, both with glomerulonephritis. Both cases were serious and discussed under SAEs.

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- **AE Dropouts in the Reproductive system and Breast Disorders SOC**

One patients discontinued because of events in this SOC. Patient 201/757-008 had endometrial hyperplasia and ovarian disorder in study 201, described under SAEs.

- **AE dropouts Respiratory, thoracic and mediastinal Disorders SOC**

Three patients discontinued drug treatment because of an AE in this SOC in the DAC HYP database, with the 150 mg dose. All three events were considered to be drug related by the investigator. Two of them were serious (301/239-001, pulmonary embolism and 303/611-029, pulmonary sarcoidosis), and one was not. The “non-serious” case (203/563-001) refers to a case of “mild alveolitis” after 5th dose of DAC in 203. The patient continued receiving DAC and developed two serious AEs after 13 doses of DAC in study 203: an event of goiter (Day 371) and an event of idiopathic pulmonary fibrosis (Day 456). All three AE dropouts have already discussed under SAE.

- **AE dropouts in the Skin and Subcutaneous Disorders SOC**

A greater number of patients discontinued because of AE in this SOC in the DAC HYP treatment groups as compared to placebo and IFN in the controlled trials. The percentage of patients who discontinued because of an AE in this SOC in study 201 was 1.4% in each of the DAC HYP groups and vs. zero on placebo. Events were alopecia, maculopapular rash and exfoliative dermatitis on DAC150, dermatitis allergic, rash and erythema nodosum on DAC300. *There was no evidence of dose response in study 201.*

The percentage of patients who discontinued because of skin event in 301 was 4.7% and 0.8% in the DAC150 and IFN β 1a group, respectively. AE leading to drug withdrawal in study 301 are summarized below.

Table 43. AE leading to drug withdrawal in study 301.

	DAC150 N=919		IFN N=922	
	n	%	n	%
Any Event in SKIN AND SUBCUTANEOUS TISSUE DISORDERS	43	4.7	7	0.8
ACNE	1	0.1	0	0
DERMATITIS	3	0.3	1	0.1
DERMATITIS ALLERGIC	2	0.2	1	0.1
DERMATITIS ATOPIC	1	0.1	0	0
DERMATITIS CONTACT	1	0.1	0	0
DERMATITIS EXFOLIATIVE	1	0.1	0	0
DYSHIDROTIC ECZEMA	1	0.1	0	0

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ECZEMA	1	0.1	1	0.1
ERYTHEMA	1	0.1	0	0
ERYTHEMA MULTIFORME	1	0.1	0	0
ERYTHRODERMIC PSORIASIS	1	0.1	0	0
EXFOLIATIVE RASH	2	0.2	0	0
LEUKOCYTOCLASTIC VASCULITIS	1	0.1	0	0
LICHEN PLANUS	1	0.1	0	0
LICHENOID KERATOSIS	1	0.1	0	0
MECHANICAL URTICARIA	0	0	1	0.1
PITYRIASIS RUBRA PILARIS	1	0.1	0	0
PRURITUS	0	0	1	0.1
PSORIASIS	2	0.2	1	0.1
RASH	4	0.4	2	0.2
RASH ERYTHEMATOUS	1	0.1	0	0
RASH MACULAR	1	0.1	0	0
RASH MACULO-PAPULAR	7	0.8	1	0.1
RASH VESICULAR	1	0.1	0	0
SEBORRHOEIC DERMATITIS	2	0.2	0	0
SKIN EROSION	1	0.1	0	0
SKIN EXFOLIATION	2	0.2	0	0
TOXIC SKIN ERUPTION	1	0.1	0	0
URTICARIA	3	0.3	0	0
URTICARIA PIGMENTOSA	1	0.1	0	0

Source: study 301, MO using Empirica Study.

There is a clear imbalance on the number of events leading to drug withdrawal in this SOC. Most events were in the Dermatitis and eczema HLT, Rashes and exanthemas HLT and Psoriatic conditions HLT (analyses not shown).

Cumulative rate of skin events leading to drug withdrawal in study 301 are shown below.

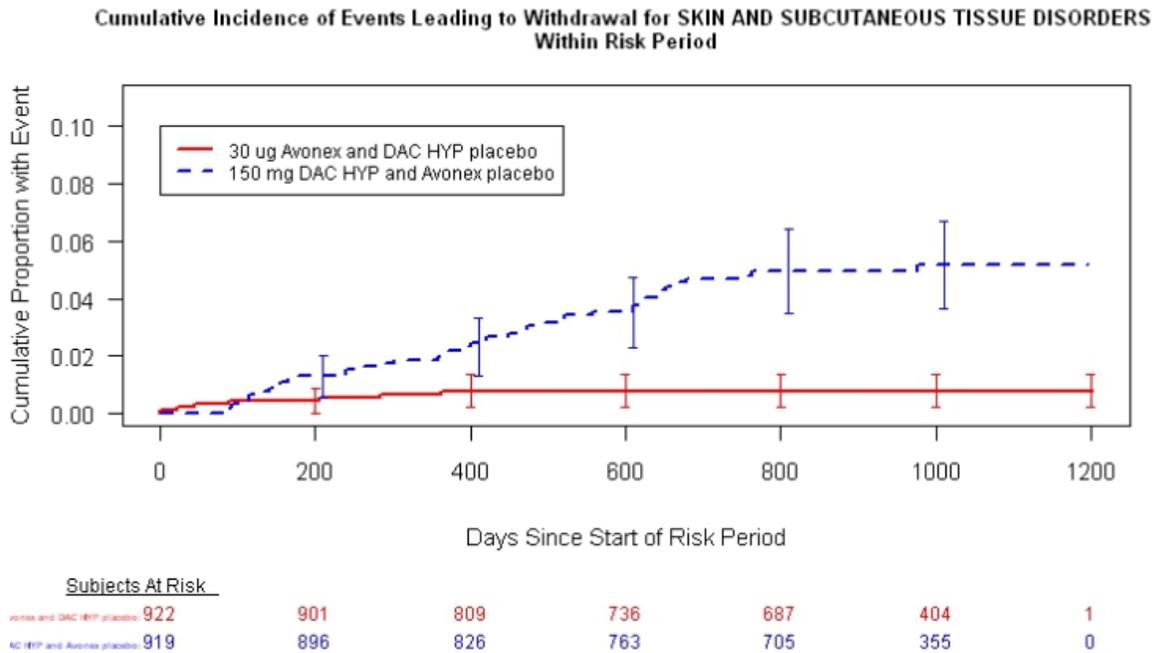
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Figure 3. Cumulative incidence of events leading to drug withdrawal in Skin and Subcutaneous tissue disorders SOC, study 301



This analysis suggests that patients started to drop out after 3 months of treatment, and continue to drop up to approximately 2 years into treatment with a cumulative rate close to 5%.

The overall rate of skin reactions leading to drug discontinuation in the total DAC HYP database was 4% (88/2236) (see table below).

Table 44. AE dropouts the Skin and Subcutaneous tissue disorders SOC

	All DAC HYP N= 2236	
	n	%
Patient with events in this SOC	88	3.9%
Rash maculo-papular	13	0.5%
Dermatitis allergic	10	0.6%
Rash	9	0.4%
Eczema	5	0.4%
Psoriasis	5	0.2%
Toxic skin eruption	5	0.2%
Dermatitis	4	0.2%

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Dermatitis exfoliative	3	0.2%
Drug eruption	3	0.1%
Skin exfoliation	3	0.1%
Urticaria	3	0.1%
Dermatitis atopic	2	0.1%
Erythema multiforme	2	0.1%
Exfoliative rash	2	0.1%
Seborrheic dermatitis	2	0.1%
Acne	1	<0.1%
Alopecia	1	<0.1%
Angioedema	1	<0.1%
Dermatitis contact	1	<0.1%
DRESS ¹	1	<0.1%
Dyshidrotic eczema	1	<0.1%
Erythema	1	<0.1%
Erythema nodosum	1	<0.1%
Erythrodermic psoriasis	1	<0.1%
Leukocytoclastic vasculitis	1	<0.1%
Lichen planus	1	<0.1%
Lichenoid keratosis	1	<0.1%
Photosensitivity reaction	1	<0.1%
Pityriasis rubra pilaris	1	<0.1%
Rash erythematous	1	<0.1%
Rash generalized	1	<0.1%
Rash macular	1	<0.1%
Rash pruritic	1	<0.1%
Rash vesicular	1	<0.1%
Skin erosion	1	<0.1%
Stevens-Johnson syndrome ²	1	<0.1%
Urticaria chronic	1	<0.1%
Urticaria pigmentosa	1	<0.1%

Source: MO analysis JMP ADAE3, SUR. ¹DRESS: Drug reaction with eosinophilia and systemic symptoms ²SJS, upon review the case was consistent with DRESS.

There were 94 events in 88 patients (29 males, 59 females with a mean age of 39 years (median 40 years)). Mean time to onset of the event leading to withdrawal 492 days (median 420 days), range 31 to 1974 days. The mean and median number of doses received before withdrawal because of a cutaneous AE were 17 and 15 respectively (range 2 to 71 doses). Mean time to (reported) resolution – for those with an end date – was 101 days (median 80 days), with a range of 3 to 610 days. Of the 94 events 15 were serious and 21 had not resolved at the time of the SUR. There were various rashes, psoriasis, dermatitis, eczema. The listing of patients

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who discontinued drug because of AE but were not categorized as serious AE in this SOC is are listed in Appendix 13 (13.3.16)

Selected narratives of patients with “non-serious” rashes are shown below.

Patient **301/703-004**, 45 M, received a total of 6 doses of DAC. He presented bilateral **swelling of hands** on Day 144-145 along with **bilateral rash of hands and feet** on Day 145-187 that led to drug withdrawal. The patient had a medical history of dermatitis. At study entry his physical exam showed mild head and face dermatitis. On Day 20, after the first dose of DAC, he presented hand erythema, swelling and pain, followed by swelling of feet, lower leg and lower lip by Day 45 of DAC treatment. He was treated with ibuprofen and chlorpheniramine and events were reported as resolved by Day 71. On Day 89 he was diagnosed with Vitamin 12 deficiency (which did not resolve). On Day 140-144 he presented mild flu symptoms followed by burning sensation, swelling and rash of hands reported as nummular **eczema and allergic urticaria leading** to drug WD. The last dose of DAC HYP was on Day 145. The rash was reported as resolved on Day 187. He had **recurrent fever** on Days 337 to 366 and flu symptoms again on Days 505-509. Concomitant meds included prednisone Day 362-367 for allergic reaction. Patient started IFNβ1a as alternative MS treatment on Day 194 to end of study (for MS).

Patient had skin rash on hands and feet along consistent with eczema, but lip, hands and feet swelling preceded and accompanied by flu-like symptoms. The clinical picture is consistent with an allergic drug reaction in a patient with underlying atopia exacerbated by DAC.

301/666-007. 43 F, psoriasis vulgaris of moderate intensity on Day 557, preceded by contact dermatitis. Hyperthyroidism was diagnosed on Day 551, and was not resolved as of the SUR. Drug WD after 20 doses of DAC. Event of psoriasis is said to have ended after by Day 735 (178 day duration). *As per the concomitant medications datasets this patient underwent several diagnostic tests including a skin biopsy on Day 559 and fungal cultures on Day 734 (the day before the event was reported as ended) for evaluation of Acute Generalized Exanthematous Pustulosis (AGEP). Beyond the fact that this AE is not in the datasets, the case underscores the difficulty in clinically differentiating a common disease such as psoriasis, from a serious skin reaction with completely different prognosis and treatment.*

Overall, at least 20 skin reactions that were non-SAEs but led to study withdrawal were still unresolved at the time of the SUR. Of the events with an end date, duration of event was from days or weeks to several months. In response to a request for information submitted on September 30, 2015, four of the events that were unresolved at the time of the SUR were still unresolved. The rest had resolved but there was no information as to whether they required persistent treatment or not.

- AE Dropouts in Vascular System disorders SOC

There were two dropouts because of events in this SOC.

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201/752-010 WD because of a SAE of circulatory collapse after one dose of DAC HYP 300.

Described under SAE of hypersensitivity and 301/606-019 Withdrawn because of non-SAE of exfoliative dermatitis/erythroderma and vasculitis, described under dropouts because of Skin reactions.

In addition to the patients withdrawn, 5 patients underwent treatment interruption, as follows

301/660-008	VASCULITIS	37 F, after 34 doses of DAC 150. Duration Day 246-253 that became serious on Day 254-277. Drug treatment continued. Patient developed erythema multiforme in study 303.
202/365-002	POLYARTERITIS NODOSA (PAN)	40 F, after 53 doses of DAC, including DAC HYP 300. Duration Day 652-696. Other AE in 202 as per datasets: fever, bronchitis, pansinusitis; later in 203: non-serious AEs of “local swelling” (verbatim “swollen legs”), diarrhea (that lasted 3 months since Day 1490) and Crohn’s disease (on Day 1636, non-serious but led to drug withdrawal). PAN is a form of systemic vasculitis. There is insufficient information in the narrative to support a definitive diagnosis but some tests may have been done that do not appear in the narrative.
203/453-025	DEEP VEIN THROMBOSIS	54 F, after 50 doses of DAC, including DAC HYP 300. Duration Day 1334-1377
203/502-007	THROMBOPHLEBITIS	27 F, after 76 doses of DAC 150. Duration Day 1607-1647, as per datasets, occurred right after MS relapse, along with rash post anti-infective and corticosteroids.
303/104-002	HYPERTENSION	38 M, after 55 doses of DAC 150. Duration Day 1184-1189.

OVERALL CONCLUSION OF AE LEADING TO DRUG WITHDRAWAL. Evaluation of AE leading to drug discontinuation was consistent with that of SAEs and showed a signal for DILI, skin reactions, autoimmune diseases and infections. Three cases of “non-serious” TB were identified in the database. Analyses of rate of events leading to drug withdrawal are not reliable in this database.

8.4.3. Significant Adverse Events

Analyses by severity did not identify any signal that had not been previously identified by review of SAE or AE dropouts.

Analyses of AE that were severe in study 301 are shown below.

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 Table 45. Patients with Severe AEs in study 301, by SOC

	DAC150	N=919	IFNb1a	N=922
Patients with any SEVERE Adverse Event	n	%	n	%
Any event	127	13.8%	108	11.7%
Any Event except MS/MS relapse	116	12.6%	92	10.0%
General disorders	16	1.7%	24	2.6%
Nervous system (includes MS related terms)	33	3.6%	34	3.7%
Nervous system (except MS)	15	1.6%	15	1.6%
Infections	27	2.9%	12	1.3%
Investigations	15	1.6%	13	1.4%
Musculoskeletal	7	0.8%	12	1.3%
Gastrointestinal	15	1.6%	8	0.9%
Skin and SC disorders	21	2.3%	3	0.3%
IMMUNE SYSTEM DISORDERS BY 1s and 2nd SOC	11	1.2%	2	0.2%
Blood and lymphatic	9	1.0%	3	0.3%
Psychiatric	6	0.7%	8	0.9%
Injury, poisoning and procedural complications	4	0.4%	6	0.7%
Neoplasms	5	0.5%	6	0.7%

FDA MO analysis using JMP.

Analyses by severity show a slightly higher percentage of severe events in the DAC HYP group as compared to IFNb1a (overall, 15% vs 13%). The SOC with the highest % on DAC HYP were Infections (3% vs 1% on IFN), GI disorders (2% vs 1% on IFN), Skin disorders (2% vs <1% on IFN), Immune system (using primary and secondary SOC) (1% vs <1% on IFN) and blood (1% vs <1% on IFN). The SOCS with higher % of events on IFNb1a were the Nervous system (4% vs. 4% on DAC HYP) and General disorders (3% vs. 2% on DAC HYP).

Interestingly, as per protocol, all MS relapses were reported as AE in study 301. The percentage of patients with severe Nervous system disorders AEs (with or without MS relapse) was very similar for DAC HYP and IFNb1a, which suggests that DAC HYP does not worsen MS, but it does not decrease the severity of MS relapses either.

8.4.4. Treatment Emergent Adverse Events and Adverse Reactions

Summary tables of AE with incidence >2% in any DAC treatment group in studies 201 and 301 by PT, from highest to lower incidence (extracted from the analyses of all AE in the Standard JumpStart review catalog) are included in Appendix 13 (13.3.3) of this review (by the end of the section).

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Events that occurred in at least 2% of DAC at any dose and at least 1% greater than placebo or active comparator were as follows:

- In study 201: upper respiratory tract infection, pharyngitis, rash, elevated ALT, depression, respiratory tract infection viral, diarrhea, pyrexia, vomiting, constipation and injection site hematoma.
- In study 301 included (list is not complete) nasopharyngitis, upper respiratory infection, tonsillitis, respiratory infection, depression, rash, seborrheic dermatitis, dermatitis, dermatitis allergica, acne, eczema.

*While this information is helpful to estimate some events (e.g. depression was increased in both trials as compared to the comparator), **because of the extensive splitting of terms, these tables do not accurately represent the incidence of most common events associated with DAC** (e.g. rash, dermatitis, dermatitis allergic, eczema; colitis, ulcerative colitis, microscopic colitis, Crohn's; all the terms consistent with DILI that are referred to by the applicant with different terms). If this product were approved, at the time of labeling DNP should ask Biogen Idec to conduct additional analyses that pool PT that represent the same event to generate AE tables by SOC and PT, for Section 6 (Adverse events, clinical trials). That requires extensive re-coding that cannot be done by hand by this medical officer. Or analyses could be presented by HLT, for some events, such as cutaneous AEs.*

All serious and non-serious AEs

Patients with all (serious and non-serious) treatment emergent AE reported in study 201 and 301 up to 180 days after last dose of DAC HYP (or DAC placebo), are summarized below by SOC, in alphabetical order, irrespective of the applicant's attribution of causality.

Table 46. Percentage of patients with AE (all) in controlled studies 201 and 301, by SOC.

SOC	STUDY 201			STUDY 301		TOTAL DAC HYP
	PLACEBO N=204	DAC HYP 150 N=207	DAC HYP 300 N=208	IFNB1A N=992	DAC HYP 150 N=919	150 & 300 N=2236
PT WITH EVENT IN ANY SOC	78.9	72.9	76.4	91.3	91.2	83.9
PT WITH EVENT EXCL MS*	68.6	72.0	73.1	91.3	88.2	81.8
INFECTIONS AND INFESTAT	43.6	50.2	53.8	56.7	64.7	59.0
NERVOUS SYSTEM DISORD	49.0	37.2	35.1	63.2	54.2	46.6
NERVOUSSYSTEME EXC. MS*	17.6	19.3	19.7	36.3	34.3	28.0
GENERAL DISORDERS	14.7	14.0	18.3	56.3	38.0	27.7
SKIN & SC TISSUE DISORDER	13.2	17.9	21.2	19.0	37.3	32.9
MUSCULOSKELETAL	17.6	12.6	13.5	28.5	30.9	25.3

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SOC	PLACEBO N=204	DAC HYP 150 N=207	DAC HYP 300 N=208	IFNB1A N=992	DAC HYP 150 N=919	150 & 300 N=2236
GASTROINTESTINAL	11.3	15.9	14.4	23.2	30.5	25.0
INVESTIGATIONS	10.8	12.1	14.9	24.0	25.5	23.0
PSYCHIATRIC	5.4	11.6	16.6	18.1	18.3	16.0
RESPIRATORY, THORACIC	6.4	4.8	6.7	14.0	16.8	12.6
INJURY, POISONING	6.4	7.7	5.3	12.9	14.9	13.0
BLOOD AND LYMPHATIC	2.9	6.8	4.3	9.5	14.1	12.1
EYE DISORDERS	3.9	3.9	4.8	9.2	9.7	8.3
REPRODUCTIVE & BREAST	3.9	5.3	5.8	6.6	8.2	7.8
EAR & LABYRINTH DIS	3.9	1.4	3.4	5.7	7.3	5.5
RENAL AND URINARY	3.4	1.9	3.4	7.3	7.4	6.8
NEOPLASMS	1.0	1.4	2.9	3.7	4.8	4.7
VASCULAR DISORDERS	4.4	4.3	3.4	6.4	4.1	5.6
METABOLISM DISORDERS	2.0	1.0	1.4	4.0	3.8	3.8
CARDIAC DISORDERS	2.0	2.9	1.0	4.2	3.9	3.4
IMMUNE DISORDERS	1.5	0	0.5	2.2	2.9	3.1
ENDOCRINE DISORDERS	0.5	1.0	1.9	2.5	2.6	3.0
HEPATOBIILIARY DISORDERS	2.0	2.9	1.0	1.7	2.8	3.7
SOCIAL CIRCUMSTANCES	0	0	0	0.1	0.5	0.1
SURGICAL & MEDICAL	0	0.5	0	0.2	0.5	0.4
CONGENITAL	1.0	0.5	0	0.1	0.5	0.6
PREGNANCY, PUERPERIUM	0.5	0	0	0.5	0.3	0.2

MO analysis. Empirica Study. May 14, 2015 datasets for individual studies, up to 180 days post last dose. Total DAC, MO analysis with JMP. Patients with events except MS estimated using ADEM datasets using JMP. MS PTs: multiple sclerosis, multiple sclerosis relapse, relapsing remitting multiple sclerosis and progressive multiple sclerosis.

The total number/percentage of patients with at least one AE was balanced among treatment groups in each of the controlled studies. The percentage was greater in 301 as compared to 201, consistent with a longer duration of treatment. Other than the Nervous system disorders, the SOCs with the greatest number of events in both studies were Infections and Infestations, General disorders and Skin and subcutaneous disorders. In general, other than the Nervous system, rates were higher in the DAC groups as compared to placebo and IFNβ1a, except for a few SOCs (e.g. Musculoskeletal disorders in study 201; General disorders in study 301). Of note, the analyses of Immune system disorders were based on the Primary SOC. The analyses are missing a substantial number of relevant terms, such as ulcerative colitis and psoriasis which were coded to the GI disorders and Skin and S.C. disorders, respectively, but for which the Immune system disorders is a secondary SOC. Analyses of Immune system disorders using the

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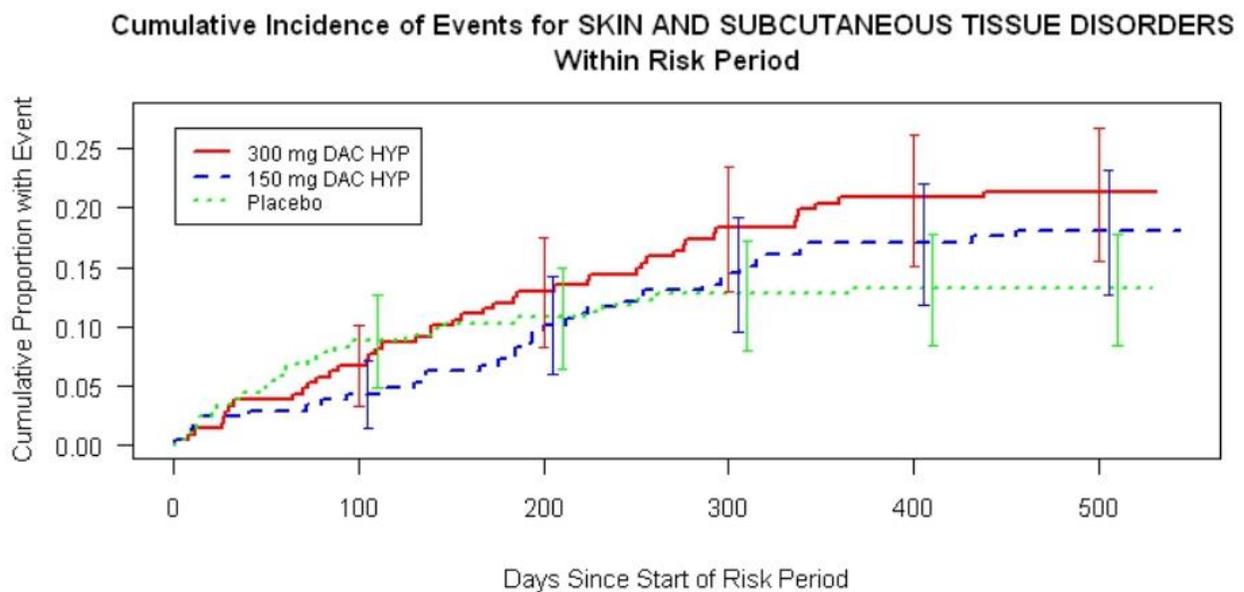
primary and secondary SOC showed a rate of 18% vs 11% in the DAC150 and IFN β 1a groups, respectively, in study 301 (See Section 8.5.3 of this review).

Cumulative rates of AE in selected SOCs are shown below.

Skin and subcutaneous tissue disorders

A total of 13%, 16% and 18% of patients presented AE in this SOC in the placebo, DAC 150 and DAC 300, respectively. Time to event analyses of all skin events in controlled trials are shown below.

Figure 4. Cumulative rate of events for Skin and Subcutaneous tissues disorders. Study 201



There is no major difference with placebo in the rate of Skin and SC tissue events within the first year of treatment.

In study 301, a total of 343 (37%) and 175 (19%) of patients presented AE in this SOC in the DAC 150 and IFN β 1a groups, respectively.

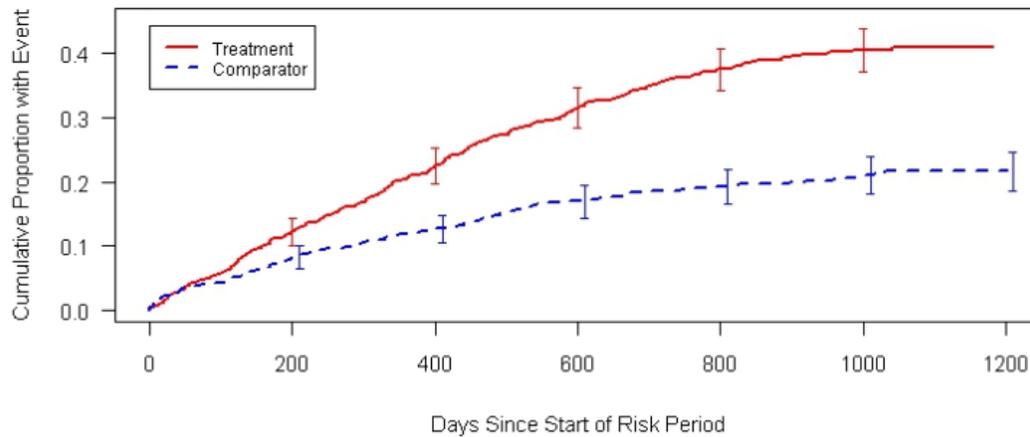
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Figure 5. Cumulative rate of events for Skin and Subcutaneous tissues disorders. Study 301



Subjects At Risk							
Treatment: 919	798	659	543	469	214	0	
Comparator: 922	829	707	612	562	319	1	

Run by DR. Villalba, using Empirica Study.

There is an obvious excess of skin reactions on DAC HYP as compared to IFN. Twice the percentage of events was reported in the DAC HYP group (40%) as compared to IFNβ1a (19%). Skin reactions occurred at any time during the study. Curves separate after 3 months but are statistically significantly different after 200 days. Moreover, 43 of the 343 (12.5%) of patients with any skin reaction dropped from DAC150 because of AE in this SOC, while only 7 of the 175 (4% of patients with any skin reaction) dropped from IFNβ1a because an AE in this SOC, suggesting that skin reactions were not only more frequent but also more severe in the DAC HYP group.

Analyses using MedDRA at a Glance for study 301 Skin and SC tissue disorders SOC, conducted by the JumpStart team by HLT showed that the most common HLTs were Dermatitis and eczema; Rashes eruptions and exanthemas; papulosquamous conditions and psoriatic conditions. A signal for an increased risk with DAC150 was observed for most HLTs. These analyses are included in Appendix 13.3.16 of this review (after the listings).

AE in General disorders and Administration site conditions SOC

There were no major differences between DAC HYP and placebo in the rate of events in the General disorders SOC in study 201. This SOC includes flu-like symptoms and injection site reactions. There was no difference in the incidence of influenza-like illnesses or overall local reactions for DAC HYP as compared to placebo (data not shown). Analyses by HLT done by this MO showed a similar distribution of events among treatment arms, except for the Febrile disorders HLT (Pyrexia) (same as the number of pyrexia AEs)(data not shown).

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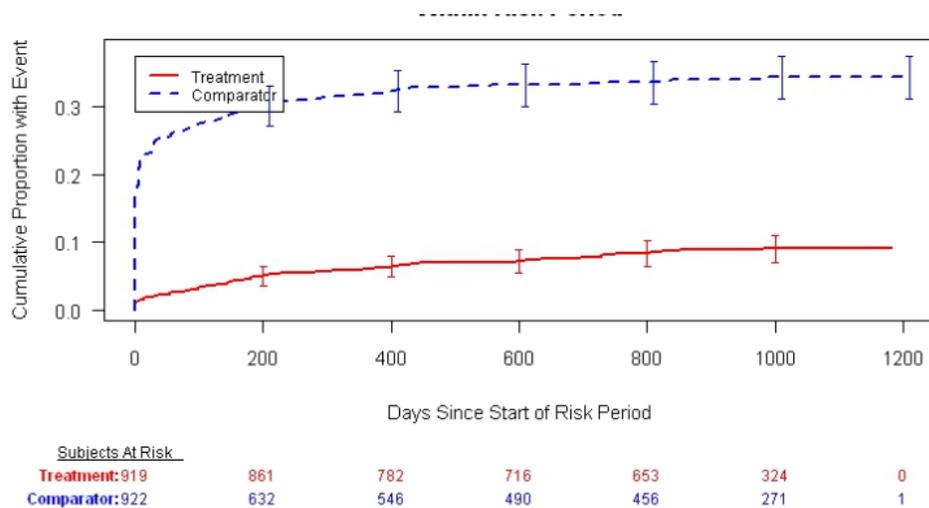
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Analyses of General disorders in study 301, showed an excess of events in this SOC in the IFN group (56%), as compared to DAC HYP 150 mg (38%), driven by the influenza-like illness preferred term (34% on INF vs 9% on DAC HYP 150). Other AE with greater risk on IFN were pyrexia (14%, vs 11% on DAC), chills (4% vs. 15 on DAC and asthenia (6% vs. 4% on DAC). Otherwise, individual events in this SOC were similarly distributed among treatment groups, with differences <1% between arms (Data not shown), but edema-related terms and chest pain/chest discomfort/non-cardiac chest pain, were more frequent in the DAC HYP group. Time to influenza-like illness is shown below.

Figure 6. Time to onset of influenza like illness, study 301



Source: Empirica study analysis (SDTM).

Time to onset of influenza like illness for IFN is early (within first 3 months). Patients on IFN are likely to have realized the treatment arm they were on because of the flu-like events, particularly if they had received IFN prior to this trial (which occurred in approximately 40% of patients in this trial).

Evaluation by HLT using JUMP in study 301 showed that the incidence of AE in Injection site reactions HLT was a similar between IFN and DAC HYP (overall 165/922 (18%) vs 155/919 (17%) in the IFN and DAC 150, groups, respectively). Individual reactions were slightly more common on IFN, except for injection site hematoma and hemorrhage that were slightly higher with DAC HYP. AE in the Pain and discomfort HLT was slightly greater in the DAC HYP group (63, 7%) vs 45, 5%). (Data not shown). Edema and peripheral edema were more frequent in the DAC150 group as compared to INFβ1a. For instance, peripheral edema was 2% on DAC 150 and 0.9% on INFβ1a. *There are no narratives for most of these cases. Because of extensive splitting of terms involving edema, additional information regarding events of edema as well as renal function and proteinuria in those patients was requested. Please refer to the discussion related to total protein and albumin and to urinalysis in Section 8.4.5 of this review..*

Other AE of interest: AE in Nervous system disorders SOC

Table 47. Summary of serious and non-serious AE in Nervous system SOC

	Study 201			Study 301		Total DAC HYP 150 & 300 N=2236
	DAC150 N=207	DAC300 N=208	Placebo N=204	DAC150 N=919	IFNb1a N=922	
All Nervous System SOC	37.2%	35.1%	49.0%	54.2%	63.2%	46.6%
Nervous S except MS*	19.3%	19.7%	17.6%	36.6%	34.3%	28.0%
Seizures HLGT	0.5%	0.0%	0.5%	1.2%	0.3%	0.9%

All AE in SOC from Empirica study. . Analyses of AE except MS done with JUMP. MS* excludes MS, MS relapse, Relapsing MS, Progressive MS

Overall, 19 patients presented an AE in the Seizures (inch subtypes) HLGT in the Total DAC database (0.9%). PT included in this SOC included epilepsy, convulsion, partial seizures, complex partial seizures, grand mal convulsion and status epilepticus (as per FDA MO analysis using JMP). Analyses of seizures in study 301 are shown below.

Table 48. Summary of serious and non-serious seizure events in study 301

PT	IFN β1a N=922	%	DAC 150 N=919	%
ANY SEIZURE RELATED	3	0.3	11	1.2
Complete partial seizure	0	0	1	0.1
Convulsion	1	0.1	6	0.7
Epilepsy	1	0.1	4	0.4
Partial seizure	1	0.1	1	0.1.
Status epilepticus	0	0	1	0.1

MO analysis. ADAE study 301. May 14, 2015 submission.

The listing of patients with seizures is included in Appendix 13.3.13 of this review. Review of the narratives did not find any particular characteristic or risk factor among patients with seizures receiving DAC HYP as compared to those receiving IFNb1a. The narratives are somewhat incomplete because they do not include full information about electrolyte/glucose abnormalities that could cause seizures (e.g. hyponatremia, hypoglycemia). As mentioned earlier, glucose was not routinely measured in clinical trials, but glucose measurements are also missing in cases where it evaluation was important (such as in the case of seizures).

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None of the SAE of seizure in 301 had a previous history of seizures. Of the 6 cases on DAC 150, 2 appear related to MS relapse or worsening MS but 4 do not appear to be related to worsening MS, while the two patients on IFNβ1a are very likely related to worsening of MS.

The label for IFNβ1a mentions the increased risk of seizures in the W&P section of labeling. The risk of seizures with daclizumab is higher than with IFNβ1a in study 301, and if approved, should also carry a warning for seizures.

Serious and non-SAE in Neoplasms SOC

Study 301

In study, 44 (4.8%) and 34 (3.7%) patients presented an AE in this SOC for DAC and for IFNβ1a, respectively. Of those, 10 (1.1%) and 8 (0.9%) were malignant for DAC and for IFNβ1a, respectively.

The difference between the rate of AE in this SOC was driven by events in the Cutaneous neoplasms benign HLGT (10 patients [1.1%] on DAC150 vs. 1 [0.1%] on IFNβ1a), Reproductive neoplasms female benign (13 patients [1.4%] on DAC150 vs. 6 [0.6%] on IFNβ1a), and other benign neoplasms (Hepatic and biliary neoplasms, Miscellaneous and site unspecified neoplasms and Soft tissue neoplasms, with 3 patients in each HLGT for DAC150 vs. 1 patient with an event in the Hepatic and biliary neoplasm benign HLGT for IFNβ1a).

Analyses by HLGT are presented in Appendix 13.3.12 of this review, for study 301 and the Total DAC HYP database.

Analyses of AE depending on cutoff used for analyses

Given the long-term pharmacodynamics effects of DAC HYP, AE analyses in this program used 180-day post-last dose cutoff. I conducted analyses of AE with cutoff at 180 days post-last dose versus 30 days post-last dose for study 301 (using Empirica Study). There were no major differences between analyses made at 180 days or 30 days post-last dose for the overall number of AEs. However, the 180-day analysis captured a greater percentage of SAE with DAC HYP (21.2% with 30-day post-dose analysis vs. 24% with 180-day post-dose) while the number of SAE with IFNβ1a was unchanged.

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Table 49. Disposition of patients in Study 301 by cutoff used post-last dose.

	180 days cutoff				30 days cutoff			
	IFNβ1a		DAC150		IFNβ1a		DAC150	
Subjects in study/pool	922		919		922		919	
Subjects with serious adverse events during time frame	194	21.0%	221	24.0%	192	20.8%	195	21.2%

Empirica study (SDTM database submitted 5/14/1015). * One or more subjects were found to have multiple disposition records. When possible, the disposition was determined using disposition date.

The analysis confirms that serious events continue to occur up to 180 days of last dose, and that should be the minimum follow up for patients after stopping DAC.

Adverse events in subset of patients using alternative MS treatments

As per the ADAE3 dataset, thirty eight patients presented treatment emergent AE that occurred within 180 days of last dose of DAC and after starting alternative MS medications in the Total DAC database. Of those, 9 patients were taking medications “other than IFN” while the event occurred (dataset does not say which agent). The nature of adverse events in these patients was consistent with those presented in patients on DAC HYP not using alternative MS medications (data not shown). SAE among patients using alternative therapy after stopping DAC HYP included one fatal aspiration pneumonia and sepsis in a patient taking azathioprine, one non-fatal septic shock in a patient with aspiration pneumonia who had been on IFNβ1a and one case of immune hemolytic anemia in a patient treated with IFN. *The database is small to draw any conclusions regarding use of MS medications after stopping DAC HYP.*

8.4.5. Laboratory Findings

Hematology

Routine hematology included Hemoglobin, hematocrit, MCV, WBC, differential WBC (eosinophils, basophils, neutrophils, monocytes) and platelet count. Conclusions regarding these parameters are provided below. Selected analyses and tables regarding these evaluations in the controlled studies are included in Appendix 13 of this review (13.3.17).

- Total White blood cell counts and lymphocytes

Analyses of changes from baseline in Mean and Median values for total WBC did not identify significant differences between DAC HYP and placebo or interferon treatment in studies 201 and 301, respectively.

The Total DAC database showed:

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A slight decrease in lymphocyte count (by 5-7% after week 144, through the last available visit, 9% at week 288); a slight increase in neutrophil counts (by 2 to 12%, with increase of 6% at week 288); a consistent increase in monocytes, first observed at week 12 (mean increase of 10% up to 23% at week 240, and by 9.5% at week 288); an increase in basophils by 20-40% throughout the study and an impressive increase in % eosinophil values, with 20 - 40% increase throughout the study, up to 80% increase at week 264, and 55% at week 288.

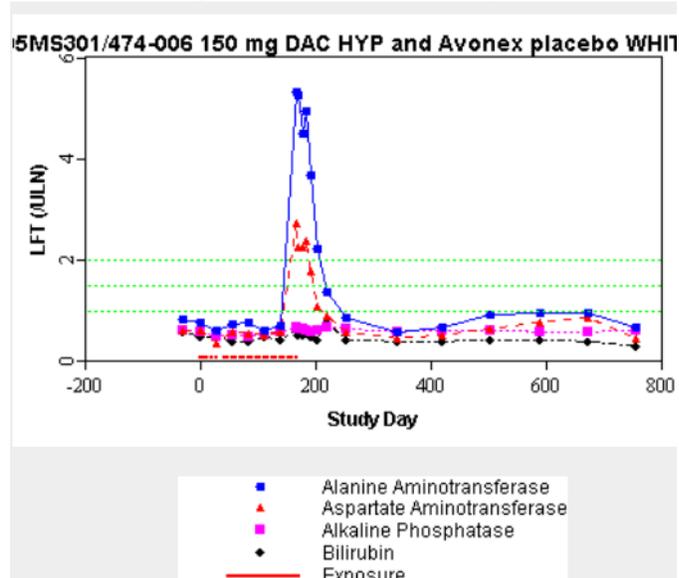
- Analyses of eosinophils.

Given the number of allergic, immune mediated and hypersensitivity reactions observed in this database, it was important to evaluate whether DAC HYP was associated with eosinophilia. Analyses showed no clinically meaningful differences in mean changes from baseline on eosinophil count between DAC HYP and placebo or IFN (data not shown).

Outlier analyses of eosinophils were submitted as part of a June 5, 2015 response to FDA. As per this response, the number of subjects with elevations in eosinophils was low and balanced across placebo, IFN beta1a and DAC treatment groups. In the majority of the cases, the elevation in eosinophil count(s) was isolated, and not persistent in nature (data not shown). Patients with eosinophil counts exceeding $1.5 \times 10^9/L$ included the following:

301/474-006 – had a single abnormal eosinophil count on day 253. Also had ALT 5x ULN. The applicant states that the patient was WD from the study for logistical reasons “*not because of eosinophilia.*” *As per Empirica Study, the last dose of DAC HYP was on Day 169 (5/2/2012). On that date, ALT was elevated 5xULN. Action taken was drug WITHDRAWN. ALT came to normal on Day 253. Concomitant meds included gabapentin and metformin, which he was taking for a long time prior to entering the trial. He did have slight eosinophilia at baseline ($0.86 \times 10^9/L$ at screening (normal range up to 0.57), but the value came down to 0.06 on Day 185, and up to 2.7 on Day 253 (8/13/2012). Workup showed negative ANA and viral testing. He had a positive anti-smooth muscle antibody (ASMA) of 1:40. The end of study day was Day 757 (12/30/2013). The events of eosinophilia and ALT elevation appear temporally related; in view of +ASMA, this could be consistent with AIH.*

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303/611-029 – had a single abnormal count on Day 1 of study 303 but no abnormal counts thereafter. This patient was diagnosed with pulmonary sarcoidosis on Day 1023. *Narrative for this patient is included in Appendix 13.3.15 of this review. The patient had symptoms consistent with sarcoidosis in study 301, but was not diagnosed until after the first dose in 303.*

301/745-001 – had borderline high eosinophils at baseline and multiple abnormal eosinophil counts up to $2.8 \times 10^9/L$ from Day 253 to end of study. He developed a lichenoid reaction after 17 doses of DAC, with chronic dermatitis and vasculitis. Eos continued to be elevated more than 2 years after drug discontinuation. *In this case eosinophilia was present in a patient with dermatitis and vasculitis and was likely related to DAC HYP.*

201/769-001 – had single elevation on Day 226 of 201. She was diagnosed with a non-SAE of photodermatosis in study 202, on Day 987 after 34 doses of DAC. *It is unclear if photodermatosis and eosinophilia were related.*

There does not appear to be an association between eosinophilia and AE in this analysis provided by the applicant. However, an upper level of $1.5 \times 10^9/L$ is a pretty high bar. In reading the narratives I identified a few patients with reported eosinophilia (301 606-020 with Kawasaki syndrome), 301/512-006 reported to have rash and slight pancreatitis, 202/301-010 (drug eruption, atypical pneumonia, mediastinal lymphadenopathy (eos 0.9×10^9 ; normal range <0.4), 303/512-009 (inflammatory rash, fever, eosinophilia (25% as per the narrative), mild ALT elevation). All these cases were suspected of DRESS. At least 2 of them were treated with high dose corticosteroids or plasmapheresis. It is unclear if those labs were captured in the datasets.

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Analysis have been requested using a threshold that is more reasonable than the submitted analyses, such as $>0.7 \text{ cell} \times 10^9 / \text{L}$ or percentage $>7\%$. A response submitted on 3/3 16 is summarized below.

Table 50. Eosinophil abnormalities, in controlled studies.

Number of

Number of

Number of

Number of

Number of

NOTE: Numbe

As per this table, there were no differences in the rate of eosinophil abnormalities in study 201. If something, the rate was higher on placebo than active treatment. Of note, the rate of eosinophil abnormalities in study 301 was higher with IFN β 1a as compared to DAC150.

The majority of the AEs presented during the time interval of 15 days prior and up to 35 days after the elevated eosinophil count were related to cutaneous events. None were related to acute hypersensitivity or anaphylactic reactions. SAE among patients with eosinophil count $>0.7 \times 10^9 / \text{L}$ not captured with the analyses made with a greater cut off were :

202/304-001: dermatitis exfoliative, on day 686 of DAC150, after 21 doses of DAC. A dermatologist suspected disseminated herpes simplex and treated the patient with acyclovir. The rash progressed to the rest of the body, including palms and oral mucosa followed by fever and chills. CRP was 39 mg/L (normal up to 10). Serum creatinine on DAC 694 was 141 $\mu\text{mol/L}$ (normal up to 110). He is reported to have elevated serum creatinine at screening. DAC150 was stopped. He was treated with topical corticosteroids and azathioprine. The event is listed as resolved. Duration of treatment for exfoliative dermatitis is unknown.

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301/512-002 developed toxic dermatitis after 4 doses of DAC HYP. Initially reported as non-SAE, it was eventually considered a SAE on Day 171. Eosinophilia of 10.5% reported on Day 170. On the day before event onset, the subject was taking desogestrel and ibuprofen. No skin biopsy was done. The subject was treated with multiple topical and systemic corticosteroids and antibiotics. The event (dermatitis) was reported as resolved.

These two cases are additional examples of rashes that may progress to serious events. If a patient on DAC HYP develops a rash, perhaps it would be useful to obtain an eosinophil count, although most patients with rashes did not have eosinophilia. Approximately 37% of patients exposed to DAC presented a cutaneous reaction. However, eosinophilia was present in a handful of patients with a cutaneous reaction. In any case, if eosinophilia is present, DAC should be discontinued.

- Atypical lymphocytes

Analyses of hematologic laboratory measurements using Empirica Study identified an increased percentage of atypical lymphocytes on DAC HYP treatment groups as compared to placebo and IFN β 1a. (In study 201, 4%, 5% and 9% in the placebo, DAC 150 and DAC 300 groups, respectively; in study 301, 4% and 2% in DAC HYP 150 and IFN β 1a, respectively). In a response to a DNP request for information submitted on July 28, 2015, the applicant acknowledged the slight imbalance. However, the applicant stated that the large majority of subjects had a single and transient value of atypical lymphocytes. Moreover, an external hematologist consultant (b) (4) stated that due to the subjectivity in conducting the manual differential, the standard of care generally defines $\geq 5\%$ as clinically significant and none of the cases on DAC HYP were $\geq 5\%$. Additionally, as per the applicant, there did not appear to be any clear or consistent correlation between the presence of atypical lymphocytes and adverse events of special interest in subjects with more than one report of atypical lymphocytes across the DAC HYP studies.

Evaluation of AE in patients with atypical lymphocytes done by this reviewer using JReview and Empirica Study in the controlled studies confirmed that most cases represent an isolated abnormal value for atypical lymphocytes; only 3 patients on DAC HYP and one on IFN had elevated values at two time points. Review of AE did not identify any particular AE associated with the presence of atypical lymphocytes in the controlled studies.

- Basophils

Study 301: % change from baseline on basophils at week 48: -9.2% on IFN and +11.9% for DAC 150. Trend observed up to week 132: -5.1% IFN and +15.5% on DAC 150 (approx. 330 pts per arm). At last available visit, week 144 (approx. 230 pts per arm), % change was 4.3% for IFN and 15.4% for DAC HYP. These changes are of unclear clinical significance (Source: Table 263, study 301 CSR)

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- Hemoglobin and platelets

There were no differences in mean changes from baseline for hemoglobin and hematocrit between DAC HYP and placebo or IFN at week 52. At the early termination there was a slight decrease in Hb in DAC HYP groups but the differences are small. Similarly, mean values for RBC parameters (Hb, HTC, MCV) and platelets were stable in both treatment groups, with little change from baseline throughout the study. (Source: CSR for studies 201 and 301, data not shown).

Twice the percentage of patients had lower Hb and platelet counts in the DAC HYP groups as compared to placebo in 201, but the numbers are small (4% vs. 2%). The number of patients with low Hb and low platelets was similar between IFN β 1a and DAC150 (Table 264, CSR). Similar % of patients had significant hematologic lab abnormalities in both treatment groups in study 301.

In the Total DAC, Hemoglobin and platelet counts showed a mean decrease of approximately 2% from baseline. These are minor mean changes but suggest that some patients may have had a relevant decrease in Hb or platelets. There were no consistent changes in hematocrit. Analyses of significant hemoglobin and platelets showed decreased hemoglobin ≤ 100 g/L in 4% of subjects (including 6 subjects with Hb < 80 g/L), and decreased platelet counts $\leq 100 \times 10^9$ /L in <1% of subjects (including 5 with platelet count less than 50×10^9 /L).

On 4/1/16 the applicant submitted the list of patients with clinically significant hematological abnormalities using the patient ID rather than the dummy ID. No new signals were identified by review of this information.

In summary, regarding WBC analyses in the controlled trials, there was no clear effect on total WBC. DAC HYP was associated with slight lymphopenia as compared to placebo, but decrease in total lymphocyte counts did not seem greater than with IFN β 1a. However, the subset of lymphocytes affected by DAC HYP may be different from those affected by IFN β 1a. In the Total DAC database, there was a 5-7% decrease in lymphocytes noted by week 144 through the last available visit. There was no increase in the number of eosinophils in patients treated with DAC HYP as compared to placebo or IFN β 1a, but eosinophil counts increased by 30% from baseline by week 144 and by 80% by week 264 in the Total DAC database. There was also a 20% increase in monocytes and basophils in the Total DAC database, throughout the studies up to the last available visit. The clinical significance of these increases is unclear.

Chemistry

Routine chemistry included Na, K, Chloride, BUN, Creatinine, ALT, AST, ALP, GGT, BR, thyroxine

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and TSH. Studies did not include measurement of blood glucose, calcium, phosphate or uric acid in the controlled studies or their extensions. Ca and glucose were measured in study 302 (6 month, open label, 113 patients). Total protein and albumin were not routinely measured either, except for study 302. Urinalyses included blood, glucose, protein, nitrites, leukocyte esterase and ketones.

- Liver enzyme analyses

Evaluation of mean and median changes from baseline in ALT and AST in study 301 suggests an earlier increase in liver enzymes with IFN, but by week 100 the mean is slightly greater with DAC HYP 150, and by week 144 the mean value is approximately the same. For GGT there is a slightly greater increase on IFN as compared to DAC HYP. There was no increase in mean/median BR in any either treatment. There was a slight increase in ALP in DAC HYP as compared to IFN. For instance, at week 144, change from baseline in ALP on IFN was -0.6 and increased by 3 units on DAC HYP (data not shown).

- Outlier analyses of ALT

ALT analyses conducted by the JUMP START team as part of the standard analysis catalog showed a greater risk of developing substantial ALT elevation for DAC HPY as compared to placebo or IFNβ1a.

Table 51. Outlier analyses of ALT elevation in Study 201 and 301.

Liver Lab Test	150 mg DAC HYP N = 208			300 mg DAC HYP N = 209			Placebo N = 204		
	Event Count	Subject Count	% of Subjects	Event Count	Subject Count	% of Subjects	Event Count	Subject Count	% of Subjects
ALT ≥ ULN									
2x ULN	65	22	10.58	32	22	10.53	31	18	8.82
3x ULN	45	16	7.69	19	14	6.70	13	7	3.43
5x ULN	29	9	4.33	8	8	3.83	5	2	0.98
10x ULN	19	7	3.37	3	3	1.44	0	0	0.00
20x ULN	6	3	1.44	2	2	0.96	0	0	0.00

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Liver Lab Test	150 mg DAC HYP and Avonex placebo N = 919			30 ug Avonex and DAC HYP placebo N = 922		
	Event Count	Subject Count	% of Subjects	Event Count	Subject Count	% of Subjects
ALT ≥ ULN						
2x ULN	465	156	16.97	434	140	15.18
3x ULN	272	87	9.47	213	76	8.24
5x ULN	159	53	5.77	85	30	3.25
10x ULN	72	24	2.61	26	11	1.19
20x ULN	16	8	0.87	8	4	0.43

Source: SDTM LAB datasets submitted May 14, 2015. Conducted by JUMP START team.

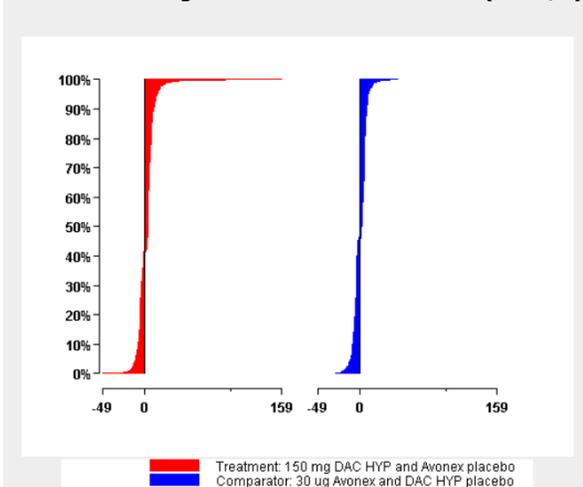
In study 201, there was no evidence of a dose response in terms of ALT elevation between DAC 150 and 300 (risk of ALT >5x ULN was approximately 4% for both DAC doses and 1% for placebo; risk of ALT >10xULN was 2-3% for DAC and 0% on placebo).

In study 301, there is evidence of a greater liver toxicity with DAC150 mg as compared to IFNβ1a, an agent known to be associated with serious liver injury. The risk of ALT >5xULN was 6% on DAC150 and 3 %, IFNβ1a; ALT> 10xULN was 3% vs 1%, respectively. In summary, the risk of developing substantial ALT elevation with DAC150 mg/day is greater than with IFNβ1a.

- BILIRUBIN (BR)

BR mean and median changes from baseline were small and similar for DAC HYP, placebo and IFN. However, there was a wider variability on BR values with DAC HYP as compared to IFN.

Maximum Change from Baseline: Bilirubin (umol/L)



In study 301, 104 patients had BR values outside the normal range (11.3%), as compared to 69 on IFN (7.5%). *The clinical significance of that finding is unclear.*

Analyses conducted with Empirica Study.

- Analyses of concomitant elevation of ALT and BR

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Patients with elevation of both ALT and BR were identified using JReview (studies 201 and 301) and eDISH (Total DAC HYP experience). Patients who appear in the right upper quadrant of these displays are referred to as biochemical Hy's Law cases. The listing of selected patients from these graphs is included below the figures with brief notes based on review of the narratives and patient profiles.

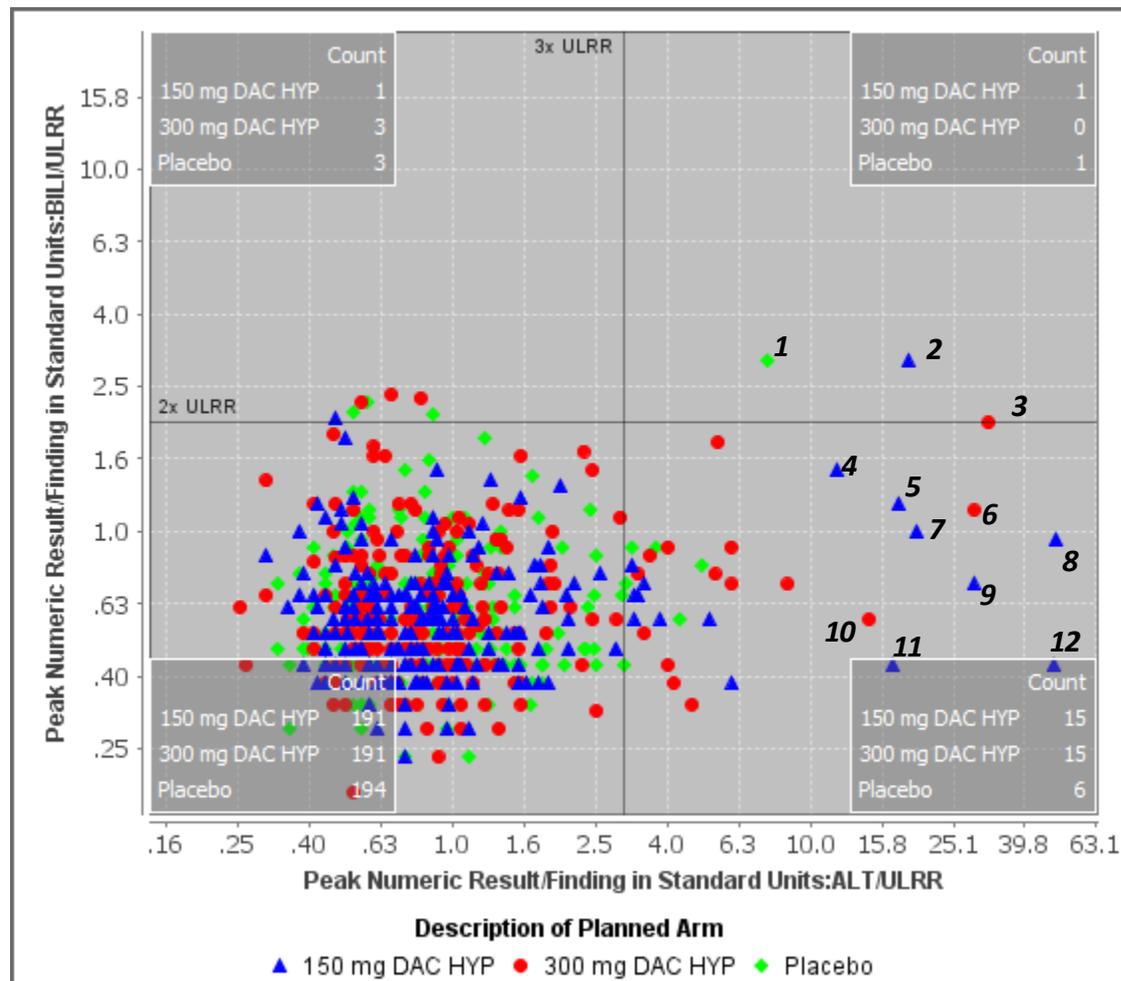
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Figure 7. Peak ALT by BR plot, without AP filter, study 201.



JumpStart. JReview. Standard analysis catalog – Hepatotoxicity (FDA.742.HEP0503 HYS Law Plot: ALT/BILI BY ARM (No alkaline phosphatase filter meaning that patients could have ALP >2xULN).

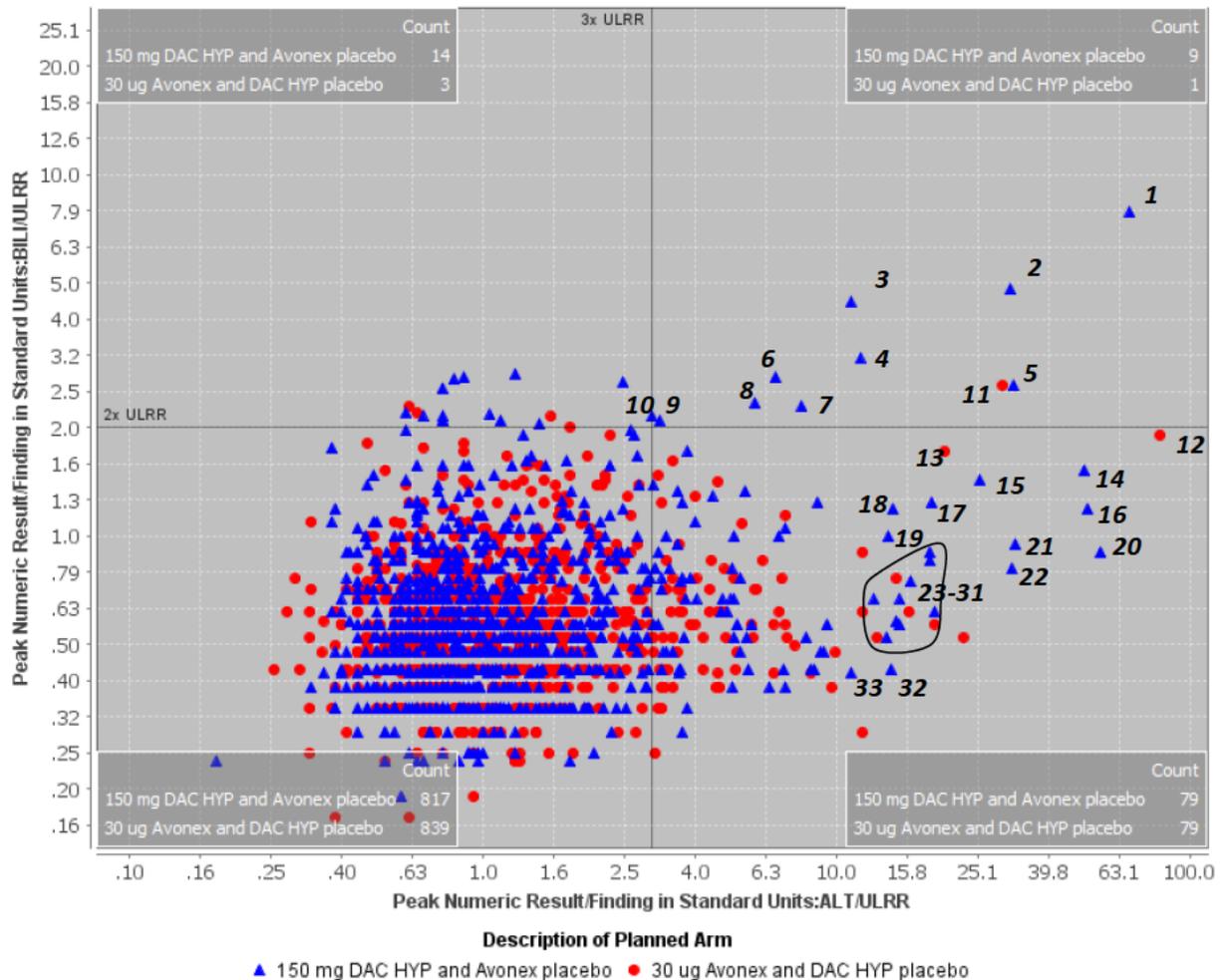
RUQ: ALT ≥ 3xULN; BR ≥ 2xULN

- 1 768-011 – Placebo: insufficient information. Gilbert’s explained elevated BR.
- 2 763-005 - DAC150: Toxic Hepatitis (hepatitis B)
- 3 454-019 - DAC300: SAE Jaundice. DILI, patient on escitalopram.

RLQ: ALT ≥ 10xULN

- 4 110-005 - DAC150: ALT increase Non SAE; SAE CMV Infection, mouth ulcers, swelling face.
- 5 761-024 - DAC150: Chronic cholecystitis resolved after cholecystectomy
- 6 752-018 - DAC300: Yersinia infection (“hepatitis form of yersiniosis” preceded by toxic skin eruption
- 7 460-010 – DAC150: Hepatic enzymes increased leading to WD (Non SAE)
- 8 763-004- DAC150: SAE Toxic allergic hepatitis confounded by use of metamizol and recent IV MP
- 9 903-025- DAC150: NonSAE increased liver enzymes. Terminated because of sponsor closed site.
- 10 908-005- DAC300: NonSAE ALT/AST increased. Did not enter extension. Resolved.
- 11 763-011-DAC150: SAE ALT/AST increased. Insufficient information. Confounded by metamizole.

Figure 8. Peak ALT by BR plot, without AP filter, study 301.



Source: JumpStart. JReview. Standard Analysis Catalog. (FDA.742.HEP0503 Hy's Law Plot: ALT/BILI no (ALP filter meaning that patients may have ALP>2xULN)

RUQ cases in study 301

On DAC 150:

- 1 624-012: Acute hepatic failure associated with serious skin rash. Confounded by CBZ & valproate.
- 2 670-024: Hepatic enzyme increased. HAC determined that it was bacterial cholangitis.
- 3 517-003: Jaundice. Gilbert's. Axillary mass.
- 4 649-006: Hepatocellular injury. Gilbert's.
- 5 604-040: Hepatitis acute. Confounded CBZ, gabapentin, analgesics
- 6 659-019: Biliary colic leading to drug withdrawal.
- 7 660-007: Reiter's syndrome, multiple antibiotic treatment and sulfasalazine
- 8 611-007: Elevated LFTs, lead to dose interruption (nonSAE). Gilbert's.
- 9 148-004: Rheumatoid arthritis, influenza like illness, treated with prednisone and Methotrexate
- 10 605-002: Elevated liver enzymes, skin exfoliation, myalgia, lymphopenia leading to WD

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On IFNβ1a:
 11 650-010: Increased ALT, AST and BR.

RLQ: CASES WITH ALT >15xULN

On DAC HYP 150

- 14 205 006 ALT increased Non SAE, drug WD
- 15 670 035 Toxic hepatitis (SAE). AIH as per consultant hepatologist.
- 16 592-001 ALT elevated Non SAE, drug WD (ALT 50xULN, concom meds. VZV infection?)
- 17 453-026 DILI (SAE drug induced hepatitis)

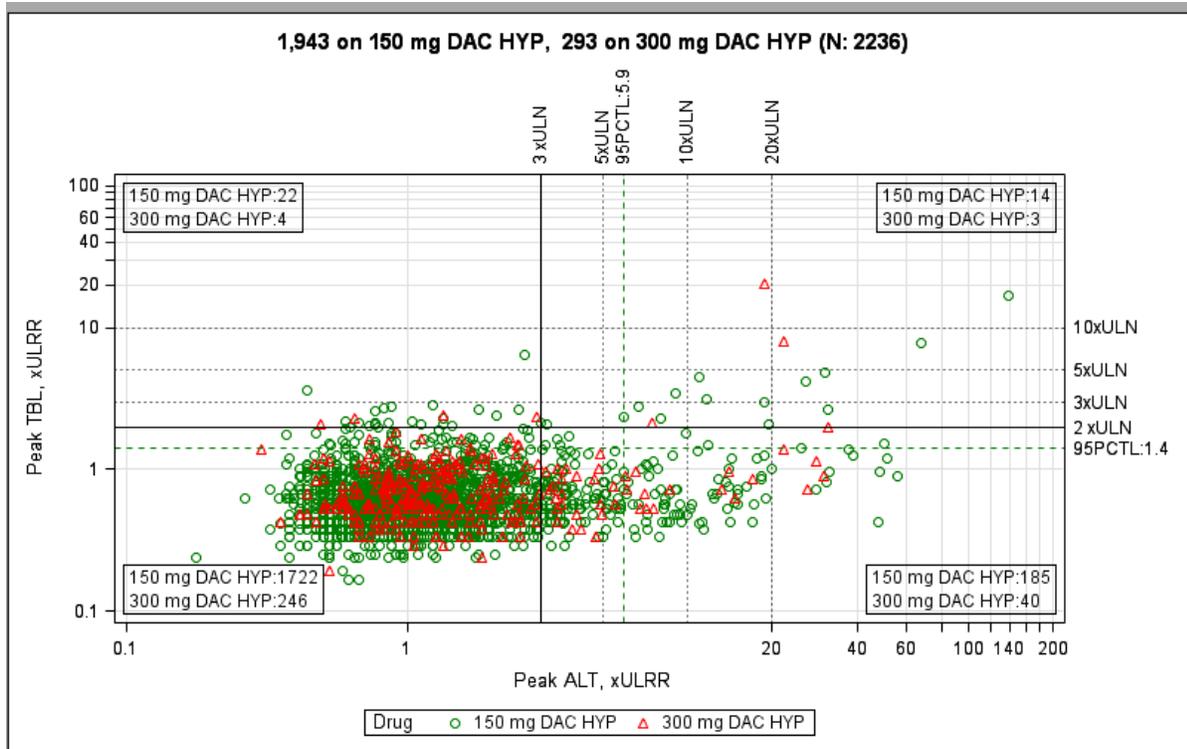
On IFNβ1a

- 12. 301 645-002 Toxic hepatitis
- 13. 301 609-021 ALT increased. Non SAE, drug WD

Evaluation of Peak ALT >3xULN by BR >2xULN using the ALP filter (<2xULN) led to very similar results, with 1 patient in each dose group in study 201 and 7 patients on DAC150 and 1 on IFN in study 301 (*data not shown*).

Peak ALT and BR analyses using the FDA eDISH in the Total DAC HYP database as of the SUR are presented below (based on eDISH datasets submitted in October 2015).

Figure 9. Peak ALT by Peak Total DAC HYP database (eDISH)



Source: FDA eDISH software.

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The figure shows 17 “laboratory defined” Hy’s law cases, 3 of which occurred in patients in the DAC300 group and 14 in the DAC150 group (some may have received IFN during study 301). In addition to the cases identified in the controlled studies, eDISH identified five patients with chemically defined Hy’s law cases in the Total DAC HYP database, as follows.

Cases with liver enzymes in biochemical Hy’s law range in DAC extension studies

202/909-001	Fatal AIH
203/453-010	ALT elevation and psoriasis, recent use of valproate
303/649-009	AIH and thrombocytopenia
203/759-008	Hepatocellular jaundice and toxicodermatosis
203/765-003	Chronic autoimmune hepatitis and thyroiditis thought to be related to PTU

Reviewer’s comment: There were few events in the RUQ (ALT and BR values in the Hy’s law range), in study 201 (the patient on DAC150 was suspected to have hepatitis B, the patient on DAC300 and the patient on placebo had Gilbert’s). However, there is a clear excess of cases with ALT >5x and >10x ULN with DAC as compared to placebo in this study.

In study 301, there is a clear excess of cases in the RUQ (10 vs 1 on DAC HYP 150 and IFNβ1a, respectively). Upon review, of the patients on DAC150, one was a biliary colic, 3 were confounded by Gilbert’s and all cases were confounded by concomitant drugs or comorbidities. Despite the confounding factors, the excess of liver enzymes in the Hy’s law range raises concern and brings up the question of whether DAC may increase the risk of hepatotoxicity with other drugs.

Additionally, more patients had increased in BR with no concurrent increase in ALT or AST with DAC HYP, in both studies. In study 201, 2, 3 and 4 patients had BR>2xULN in the DAC150, DAC300 and placebo groups, respectively at some point during treatment.

In study 301, 24 patients had BR>2 on DAC150 group as compared to 4 on IFNβ1a.

In the Total DAC database 43 patients had BR>2. This could be consistent with Gilbert’s syndrome or perhaps an obstructive component of DAC induced hepatotoxicity.

I have reviewed the narratives and patient profiles of all patients from the RUQs as well as most in the RLQ of these plots (see SAE and AE leading to Discontinuations sections of this review). Relevant cases have also been reviewed by FDA hepatologists consultants. For further discussion see Section 8.5.1 of this review.

- Analyses of NA, K, chloride, BUN, creatinine and thyroid function

Mean and median actual values for sodium, potassium, chloride and bicarbonate were submitted in the original application without the analyses of change from baseline. Upon the FDA request, the applicant submitted these analyses in June 2015.

In study 201, shift analyses of blood creatinine showed a shift to high in 3% of patients in the

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DAC150 and DAC300 groups and in 1% of patients on placebo. Bicarbonate showed a shift to higher in 7%, 2% and 3% of patients on DAC150, DAC300 and placebo, respectively. Thyroxine (T4) showed shift to low values in 5% of patients in the DAC150 and DAC300 groups, and 3% of those on placebo. Otherwise shifts to high and low for sodium, potassium and TSH showed similar changes. Mean changes from baseline in creatinine were similar in all three groups. Creatinine post-baseline abnormalities suggested there were more patients with slight increase in creatinine >1 to 1.5 ULN in the DAC groups (3% each) versus placebo (1%), but the numbers are small, and no patient presented creatinine increase above 1.5xULN.

In study 301, shift analyses to high blood urea nitrogen (BUN) was 4% in both treatment groups; shift to high creatinine values occurred in 4% of patients on DAC150 and 3% of patients on IFN (Table 55 301 CSR). Mean values and mean changes from baseline for BUN and creatinine remained stable throughout the study in both treatment groups and showed no clinically relevant changes over time.

Shifts to high or low for sodium, potassium, chloride and bicarbonate were similar in both treatment groups (<1 to 6%); if something, they tend to occur at a slightly higher rate on IFN, but there was no consistent pattern. Shifts to high or low values for TSH and Total Thyroxine were slightly higher in the DAC150 group. Analyses are shown below.

Thyr
Th
To

Source: page 312, study301 CSR)

In this analysis, 12% of patient on DAC150 had a shift to low thyroxine levels as compared to 9% of patients in the IFN group. More patients also had a shift to low TSH on DAC150 than IFN (8% vs. 5%). Similar number of patients had thyroid related AE in study 301 (3 patients in each group). Of interest, autoimmune thyroid disease is included in the Avonex label under Autoimmune disorders along with autoimmune hepatitis.

In response to a request for information, on 3/3/16 the applicant provided a table with thyroid function abnormalities in study 301, as follows.

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Table 52. Patients with thyroid function test abnormalities in study 301

Low thy
High th

NOTE: Number

As seen in this table, there is a trend for higher number of patients with thyroid function abnormalities in the DAC150 treatment group, as compared to IFN. No differences were reported in study 201.

Electrolytes, creatinine and thyroid function in the Total DAC database as of the SUR

Similar to the original application, actual values of electrolytes by visit were submitted for the Total DAC HYP database, but tables summarizing the changes from baseline were not submitted.

Review of creatinine overtime suggest a small but consistent increase in creatinine from a mean of 70 µmol/L at baseline to 73 µmol/L at week 264, with slowly increasing values in between (Table is included in Appendix 13.3.17 of this review).

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Table 53. Shift analyses of chemistry evaluations in Total DAC HYP as of the SUR

Electrolyte and renal function	Tot <u>Shift to I</u> (a)
Electrolytes Sodium Potassium Chloride Bicarbonate	5/2224 (<1) 43/2209 (2) 10/2223 (<1) 85/2214 (4)
Thyroid function Thyroid stimula hormone Total Thyroxine Free Thyroxine	89/1574 (6) 157/1516 (10) 10/569 (2)

Extracted from Table 131 of SUR.

Shift analyses of electrolyte and renal values in Total DAC HYP as of the SUR shows that 3% and 4% of patient shad shifts to high for creatinine and BUN values at least once during the trials, while only <1% had shifts to low. This potential signal on renal function is consistent with the increase in mean creatinine.

More patients also had shift to high values for sodium (6%) as compared to low values (<1%), but analyses of sodium values over time did support an increased rate of hypernatremia. Shift analyses for K, Chloride and bicarbonate do not raise any signal.

Shifts from baseline and mean changes from baseline on creatinine suggest either slight decrease of renal function or that some patients may have been dehydrated. In the absence of a comparator, this is difficult to interpret.

- Total Protein and albumin

On 2/15/16, in response to an FDA request for information, the applicant clarified that Total protein and albumin were not part of routine measurements in the phase 3 trial because no trend had been observed in prior studies. The applicant identified 3 patients with low serum total protein and/or hypoalbuminemia in the clinical program (not done as routine but during evaluation of other conditions), as follows:

202-909-001 with fatal liver failure; 302/622-103, with autoimmune hepatitis. At the time of peak ALT (days 280 -287) total protein was 58 g/L (“less than normal range”). At other times, measurement of total protein was normal; and 303/141-008, the patient with celiac disease. In addition to these patients, I have identified at least one patient with hypoalbuminemia in the

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DAC HYP program, the patient with CMV hepatitis. *These cases have been discussed previously.*

- Urinalyses

For all urinalysis parameters, the incidences of shift to high/positive test results did not show a consistent pattern in the development of abnormalities in any treatment group.

Shift analyses for Urinalyses in study 201 showed:

Blood: Negative to non-negative 43/145 (30%) on DAC 150, 58/131(44%) on DAC300, and 50/138 (36%) on placebo. *(This is not quantitative; it could be related to an infection or to a menstrual period.)*

Glucose: Negative to Non-negative 4/199 (2%), 6/200 (3%) on DAC150 and DAC300, and 3/199 (1.5%) on placebo *(It was slightly higher on DAC groups than placebo; it would have been helpful having blood glucose levels too in this clinical trial)*

Protein: Negative to non-negative DAC150: 86 (43%), DAC300: 96 (48%), Placebo: 84 (42%). *As per a response to a request for clarification received 2/15/16, "non-negative" means positive. As per response submitted on 2/15/16, more subjects with had 2+ and 3+ positive urine protein in the DAC 300 group as compared to placebo, in study 201, but the numbers are small.*

Table 54. Proteinuria in study 201

The image contains two bar charts. The top chart shows proteinuria levels for three groups: DAC 150, DAC 300, and Placebo. The y-axis represents proteinuria levels: Trace, 1+, 2+, and 3+. The DAC 300 group shows the highest percentage of subjects with 2+ and 3+ proteinuria. The bottom chart shows proteinuria levels for the Worst post-baseline group, with a similar distribution to the DAC 300 group.

Group	Trace	1+	2+	3+
DAC 150	~30%	~60%	~10%	~0%
DAC 300	~30%	~50%	~15%	~5%
Placebo	~30%	~60%	~10%	~0%

Group	Trace	1+	2+	3+
Worst post-b	~30%	~50%	~15%	~5%

Source: Table 2, 2/15/16 submission. 1 Numbers in parentheses are percentages. 2 Only subjects with non-positive baseline and at least one post baseline measurement are included.

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Shift analyses for Urinalyses in study 301 showed:

Blood: slightly more patients had abnormal blood in urine at week 48 (9% on DAC150, 7% on IFN) and week 96 (11% on DAC150, 6% on IFN). At week 144, 10% of patients on DAC150 and 9% of patients on IFN had abnormal blood in urine. *It is difficult to interpret blood present in isolation, without quantitative values or knowing whether it was associated with other signs and symptoms.*

Glucose: At baseline, 9 (<1%) and 11 (1%) had abnormal glucose present in urine in the DAC150 and IFN groups, respectively. Over time, the number of patients with abnormal glucose was close to 1% in each treatment group, at each visit. The largest difference in the number of patients with urine glucose was at week 24 (found in 12 (1.4%) of patients on DAC150 and 4 (0.5%) of patients on IFN). *There is no tabular presentation of the number of patients who had at least one urine glucose abnormal. As mentioned earlier, it would have been helpful to have routine blood glucose measurements in study 301.*

Urine protein: At baseline a slightly higher percentage of patients had abnormal protein (28% on DAC150 and 26% on IFN). A similar 2-3% difference with a little higher incidence on DAC150 was maintained over time.

The number of patients with proteinuria in study 301 was balanced between DAC150 and IFN.

Table 55. Proteinuria in study 301

Trace
1+
2+
3+
4+

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Trace
1+
2+
3+
4+

Source: Table 3, 2/15/16 submission.

Urine nitrites, leukocyte esterase and ketones were present in similar numbers of patients at each visit in study 301.

Shift analyses of urinalyses are shown below, for the Total DAC HYP database

Table 56. Shift from baseline for urinalyses in Total DAC HYP database.

NOISE. ENCE
high
leas
(a) Shift
(b) Shift

Analyses show that 4% of patients had glucosuria at least once during the studies, and more notable, that 63% of patients had urine protein. I would like to find out the extent of proteinuria, whether any of these patients had quantitative analyses and proteinuria, whether proteinuria was accompanied by blood or urine cell casts, menstrual period or urinary infection, and whether any of the patients with AE of edema in this application had proteinuria.

In a response to a request for information submitted 2/15/16 the applicant's medical review identified 38 AEs clinically relevant to proteinuria in 23 subjects. The majority of the non-serious adverse events within defined time period were urinary tract infections (26), 1 event of chronic renal failure, proteinuria (1), and hematuria, leukocyturia and proteinuria in 1 subject. There is no narrative for non-SAEs. Three subjects had SAE with associated proteinuria

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(203/109-003, Urinary tract infection; 202/505-018 mesangioproliferative glomerulonephritis; 201/559-004 nephrolithiasis and urinary infection.

Review of the information submitted on 2/15/16 suggests that most cases of proteinuria were related to infection or lithiasis. One case of significant proteinuria occurred in a patient with mesangial glomerulonephritis. This case has been previously described under SAE in the Renal disorders SOC. Apparently none of the patients with peripheral edema had proteinuria.

As per the 2/15/16 response to FDA request for information, the incidence of urine glucose abnormalities in the controlled studies was comparable between DAC HYP and placebo (2% on DAC150, 3% on DAC300 and 2% on placebo) and between DAC150 and interferon β -1a (4% each). The incidence of glucose abnormalities in the total DAC HYP was 4%. Of the subjects positive for urine glucose in the total DAC HYP database (n=82), 57 (70%) only had a single abnormal reading of glucosuria. Fifteen of the 82 (18%) had a medical history of diabetes at screening, and 49/82 (60%) had been treated with high dose pulse corticosteroids. *Therefore, 80% of patients with at least one event of glucosuria had no prior history of diabetes, and 40% had not received high dose corticosteroids. **Again, it is unfortunate that routine serum glucose was not measured in the trials.***

Overall, there are no obvious differences between DAC HYP and placebo or IFN for the hematology and chemistry parameters presented in this application (other than liver related tests). The lack of glucose and calcium measurements in these trials is a concern. These trials are likely to have under-ascertained diabetes mellitus. As mentioned earlier, given the suspicion of sarcoidosis in a substantial number of patients, it would have been useful to have calcium measurements.

Special laboratory analyses conducted by the applicant

Special lab analyses of lymphocytes subsets were conducted in study 201 and 202, showing a decrease in Tregs and increase in NK cells. CD56bright NK cells are reported to have several key immunoregulatory functions including the production of immunomodulatory cytokines and the ability to kill activated T cells. Both of these functions of CD56bright NK cells are believed to contribute to the therapeutic benefit of DAC HYP in MS [Wiendl 2013; Bielekova 2013].

The applicant proposes that because there does not seem to be a correlation between Treg levels and AEs or therapeutic efficacy, Treg cells that remained were likely “functionally competent.” I do not agree that the lack of correlation of Treg levels with AE in studies that were not designed to assess that relationship allows a conclusion that Tregs are functional. For evaluation of lymphocyte subsets the reader is referred to the FDA reviews by the Clinical Pharmacology and Non-clinical toxicology teams.

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8.4.6. **Vital Signs**

There were no clinically relevant changes in mean and median values for pulse, respiratory rate, and temperature before and after dosing and at the end of the study in the individual studies 201, 301 or the Total DAC HYP database (data not shown). Orthostatic blood pressure was not measured.

8.4.7. **Electrocardiograms (ECGs)**

No relevant ECG changes were observed in the phase 1, 2 or 3 trials of DAC HYP. (Data not shown)

8.4.8. **QT**

There was no TQTc, as effects on the cardiac conduction system are not expected.

8.4.9. **Immunogenicity**

As per section 2.7.2 Summary of Clinical Pharmacology Studies, Section 4.1.2), treatment-emergent anti-Dac antibodies (ADAs) were observed in **4%** of evaluable subjects in study 201 and **19%** in study 301. Neutralizing antibodies (Nabs) were observed in 3% of subjects in study 201 and 8% in 301. The higher incidence of immunogenicity in Study 301 was explained by more frequent testing at early time points (e.g., Week 4) (as per the sponsor “when immunogenicity to DAC HYP is more common”) and the use a more sensitive assay in study 301 as compared to the one used in 201. Among those subjects with long-term exposure to DAC HYP, the majority of subjects who became ADA-positive did so during the first year of treatment, and the immunogenicity response was transient. There was no discernible impact of ADAs or NABs on the different safety or efficacy endpoints or on the PD markers evaluated, including CD25 saturation, increase in CD56bright NK cells, and decrease in Tregs. Furthermore, subjects who reinitiated treatment in the presence of ADAs and NABs did not appear to be at higher risk for AEs than antibody negative subjects. Population PK analysis showed that time-varying NAB-positive status increased the DAC HYP clearance by an average of 19%. Additionally, as per the applicant, the immunogenicity profile of DAC HYP administered by an SC injection using the PFS was comparable to that of DAC HYP administered from the vials. “Given the absence of safety signals, as well as the transient nature of most immunogenicity” the applicant did not propose routine monitoring for immunogenicity. For additional information see the FDA Clinical Pharmacology review (which is pending at the time of this review).

As per the applicant’s analyses there did not seem to be a dose response between development of anti DAC antibodies or neutralizing antibodies between DAC HYP 150 and 300 in study 201. Anti-DAC antibodies tend to appear within the first 24 weeks, while neutralizing antibodies were less common and were spread over time. As per data provided in the SUR, 17 patients

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had treatment emergent ADA among 2236 patients exposed to DAC HYP, of whom 7 were persistent and 10 were transient; and only 7 patients became Nab positive of whom 2 were persistent and 5 were transient.

Reviewer Comment: As per discussion with Chen Su, CMC/Product Quality reviewer, via email, ADA screening assays used for studies 201 and 301 were adequately validated, including sensitivity and specificity. Moreover, a pre-existent ADA activity of 4% - 6% (as that shown in 201 and 301, respectively) is acceptable. However, the presence of daclizumab in the serum sample itself causes a diminished sensitivity for neutralizing Ab meaning that at trough levels of daclizumab, ADA positive samples that are considered not to have neutralizing antibodies may in fact have those antibodies.

From the safety point of view, there does not seem to be a correlation between the presence of anti-DAC or neutralizing antibodies and significant AEs (serious AEs or causing drug discontinuation). As per my review of individual narratives of all these cases, the great majority of patients with these events were anti-DAC and neutralizing antibody negative. An exception is the case of a patient who died of an infectious complication of a severe rash, after she had discontinued the drug because of elevated ALT. Other than that patient, a handful of patients with serious AEs were AntiDAC or neutralizing AB positive, and those were transient. In my opinion this observation would support that the immunologic adverse events observed in patients receiving DAC HYP are not DAC antibody mediated. On the other hand, if high daclizumab levels interfere with detection of neutralizing antibodies these analyses of clinical correlation are not reliable.

Immunogenicity in patients who re-started DAC

The application includes data from 498 patients who interrupted and re-started DAC treatment. Per protocol, patients could only skip one dose. If they suspended treatment for more than 1 dose were to be discontinued, except in study 202, in which a 4 month washout was part of the protocol. A total of 347 patients had a dose interruption of >2 doses. Of those, only 4 (1%) had a serious immune mediated event (two cases of colitis, one autoimmune hepatitis (the fatal case) and one exfoliative dermatitis).

Reviewer Comment: One event of colitis occurred on DAC 150, the other 3 events occurred on DAC 300. However, the data are not sufficient to conclude that DAC150 is safer than DAC300. The number of events is small and these two groups were not randomized. Moreover, patients on DAC300 had longer exposure to drug than those on DAC150.

Based on the patient who died of autoimmune hepatitis (205MS201/909-001), re-challenge with DAC HYP can be fatal. This patient had mild ALT elevation in study 201; ALT normalized in study 202 during placebo washout and increased rapidly when DAC HYP was re-introduced in the second part of study 202. Damage continued despite drug discontinuation and the patient died 3 months after the last dose of DAC HYP. Dr. John Senior has conducted a very detailed review

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of this case. It would be interesting to look at the percentage of patients who had mildly elevated ALT in study 201 and were rechallenged in 202.

8.5. Analysis of Submission-Specific Safety Issues

One of my major concerns with DAC HYP is the risk of drug induced liver injury (DILI) some of which (but not all) were diagnosed as autoimmune hepatitis.

Another major concern is the high rate of immune-related reactions observed in this application, including

- Cutaneous reactions (some of which are not unexpected –eczema, psoriasis-, but some that are drug allergy type reactions), including possible cases of DRESS and cutaneous vasculitis.
- Immune-mediated reactions (e.g. colitis, celiac disease, sarcoidosis)

I will discuss the major issues I found in the following sections: Liver toxicity, Cutaneous toxicity and Other immune mediated reactions, although some of the liver toxicity and cutaneous reactions are part of the overarching issue of immune mediated reactions.

8.5.1. Drug Induced Liver Injury

At the time of the SUR, 125 (5.6%) patients in the Total DAC HYP database had a SAE or an event that led to drug withdrawal in the Hepatobiliary or Investigations SOCs, including one who died from autoimmune hepatitis (202/901-001).

Analyses of liver related events and laboratory evaluations in study 301 show that DAC HYP is associated with greater hepatotoxicity than IFN β 1a. Five patients had SAE consistent with Drug Induced Liver Injury (DILI) on DAC150 (301/624-012, 301/110-006, 301/453-026, 301/604-040, and 301/670-035), versus 1 SAE of DILI on IFN β 1a (301/645-002) in study 301.

With the caveats discussed in section 8.3 of this review, as per the datasets, 49 (5.3%) and 36 (3.9%) patients discontinued drug because of an AE in the Hepatobiliary SOC or Investigations SOC/Hepatobiliary HLGT in the DAC150 and IFN β 1a groups, respectively. The mean number of doses that patient on DAC150 received before drug withdrawal was 18 (range 3 to 35) doses. Time to onset of an event that led to drug withdrawal was longer for DAC150 as compared to IFN β 1a (mean of 507 and 305 days, respectively).

Of note, per protocol, patients with ALT or AST >5xULN had to be withdrawn from the study. Laboratory analyses showed that the percentage of patients with ALT 5x, 10x and 20x ULN was roughly twice on DAC150 vs. IFN β 1a (ALT 5xULN in 5.8 % vs. 3.2%; ALT 10x ULN 2.6 vs. 1.2%: ALT 20xULN in 0.9% and 0.4%, respectively). The percentage of patients with ALT>3x ULN was

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slightly higher with DAC150 (9.5%) as compared to IFNβ1a (8.2%).

Analyses of ALT≥3xULN + BR≥2xULN (“biochemical Hy’s range”) in study 301 identified 9 patients on DAC150 vs. one on IFNβ1a. The course of liver enzymes and the narratives for these cases are included in Appendix 13.3 of this review (0). Dr. Avigan identified one Hy’s law case among the cases on DAC150 (301/624-012) (with a score of “Probable/Possible” related to DAC HYP). The applicant’s independent Hepatic Adjudication Committee (HAC) categorized the case on IFN as a “Highly likely” and the case on DAC150 as “Probably” related to DAC HYP. A Hy’s law case represents “pure hepatocellular injury sufficient to cause hyperbilirubinemia” and can be attributed to a drug (11). The scoring used by Dr. Avigan and the HAC is based on the Drug Induced Liver Injury Network (DILIN) scoring system and is described in Dr. Avigan’s review. Only cases with a “Probable” score or higher were considered to be Hy’s law cases.

The two Hy’s law cases in study 301 are summarized below.

ID	Summary	Confounding
301/624-012	Life-threatening drug induced acute hepatic failure from Day 197 to 241. Jaundice, hypoalbuminemia, increased INR, after 8 doses of DAC150. Bx consistent with DILI. Resolved 3 months after drug discontinuation.	Carbamazepine started Day 113 for focal partial seizure and MS relapse. On the same day erythema was noted at the site of DAC injection followed by generalized rash. Switched to valproate (VPA) on Day 127. Microvesicular steatosis characteristic of VPA-induced DILI was <u>not</u> present in liver biopsy.
301/650-010	Nausea. Non-SAE of ALT and BR in the Hy’s range from Day 113 to Day 126. Not hospitalized. Resolved within 2 weeks after drug discontinuation.	As per the HAC, alternative explanation could be spontaneous autoimmune hepatitis.

Dr. Avigan’s review of additional cases with ALT & BR values in the Hy’s range identified one patient with a “Possible” Hy’s law case (301/604-040, acute toxic hepatitis confounded by carbamazepine use), and 7 that were “Possible or Unlikely” as follows:

301/148-004 (patient with rheumatoid arthritis, influenza like illness treated with prednisone and methotrexate)

301/517-003 (Gilbert’s)

301/605-002 (with skin exfoliation, myalgia and lymphopenia),

301/611-007 (Gilbert’s)

301/649-006 (Gilbert’s),

301/660-007 (Reiter’s syndrome treated with sulfasalazine) and

301/670-024 (diagnosed as bacterial cholangitis).

Of note, determination that a case is a “Possible” Hy’s law case does not necessarily mean that

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the drug is not hepatotoxic. However, the presence of BR>2 does not have the same ominous prognosis than that of pure hepatocellular damage.

Although Dr. Avigan and the HAC scored 301/670-024 (bacterial cholangitis) as “unlikely” Hy’s law case, I believe that an immune mediated mechanism cannot be ruled out because there was lymphadenopathy in the hepatic hilum and the patient was responding to high dose steroids before starting antibiotic treatment.

As per review of the narratives, at least 2 patients on DAC150 underwent a liver biopsy (301/670-024 and 301/640-035) and 5 were treated with high dose corticosteroids for suspected AIH in study 301 (301/205-006, 301/228-003 and 301/453-041, in addition to the two patients with liver biopsy). *I did not identify any patient who needed a liver biopsy or was treated with high dose steroids in the IFNβ1a treatment group, but I did not read all the narratives for events that occurred on IFN.*

Exploratory analyses of liver related adverse events and investigations conducted by Dr. Ana Szarfman using Empirica Study Bayesian analyses in study 301 showed that the use of systemic corticosteroids and of drugs typically associated with liver failure, and prior use of IFNβ1a did not have a consistent effect on liver AE or enzymes among DAC HYP treated patients. (Data not shown). These results are in line with analyses conducted by the applicant, who did not find any particular associated risk factors. The applicant also conducted a genomic analysis and did not find any particular genotype that increased the risk of liver events.

Overall, at the time of the SUR there were 18 SAE consistent with Drug Induced Liver Injury (DILI) in the in these two SOCs. Three additional SAE consistent with DILI were submitted as IND safety reports after the cutoff of the SUR.

Additionally, some events in SOCs other than the Hepatobiliary and Investigations may have represented DILI (e.g. a case reported as arteriovenous malformation (201/509-007 with ALT 47X ULN beginning after 12 doses of DAC that resolved after discontinuation; a case of hepatic yersiniosis without supportive evidence for such diagnosis (201/752-018); two cases reported as infectious mononucleosis with negative IgM ab, and one case of celiac disease with hepatic involvement (I agree it could be celiac disease but I believe it is DAC HYP-induced). Therefore, overall, there are at least 21 SAE of DILI in this application, or 26 if SAE reported in other SOCs are also counted.

Dr. Avigan reviewed narratives of 46 serious and non-serious cases of potential DAC HYP induced liver injury in the Total DAC HYP database (13.3.6). Of those, approximately two thirds were categorized as probably or probably-possibly related to DAC HYP. In addition to the patient in study 301, Dr. Avigan identified 2 Hy’s law cases from the extension studies (202/909-001 and 303/649-009) and I identified one case that had not been reviewed by Dr. Avigan (201/454-019). These cases are summarized below.

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ID	Summary	Confounding Factors
201/ 454-019	On DAC300. Jaundice on Day 336 after 12 doses of DAC. Last dose had been on Day 308. Bx showed fulminant hepatitis, acute hepatic dystrophy with necrosis. Reported as resolved 2 months after the last dose of DAC HYP without CS treatment.	Had MS relapse and received IV MP on Day 280-283. Hydroxyzine and escitalopram started on Day 300.
202/ 909-001	Fatal hepatic failure. After 4th dose of DAC300 (following 13 doses of DAC300 in 201 and a 6-month washout period in 202). Bx showed autoimmune hepatitis. Received CS late in course of disease.	Had MS relapse and received IV MP a few days before re-starting DAC at end of washout.
303/649- 009	Autoimmune hepatitis after 4 doses of DAC150. Responded to CS treatment. Developed thrombocytopenia when CS was tapered requiring second course of CS. Resolved but follow up is short.	Had received 96 weeks of IFNβ1a in Study 301; developed autoimmune thyroiditis in 301, but liver enzymes were normal.

Overall, of the 4 Hy's law cases in the DAC HYP database two were determined to be autoimmune hepatitis (AIH) and two were not. Although there is no definitively accepted treatment, the literature suggests that high dose corticosteroids and additional immunosuppression is helpful in the treatment of AIH.

In the case of patient 202/901-001, the diagnosis of AIH was made a few days before her death, almost 3 months after the last dose of DAC HYP. The patient had not missed any of the protocol mandated monthly liver enzyme measurement. The day of her last dose of DAC HYP ALT level of 12 x ULN with normal BR (after dosing); the ALT value one month earlier was 5.7x ULN. It is possible that measurement of liver enzymes right before the next dose and discontinuing treatment if >5xULN (as implemented in the protocols after her death) could have prevented her demise. This case was described in detail in Dr. Senior's consultative review (8). His conclusions are summarized in Appendix 13.3 of this review (13.3.6).

Of note, some patients with significant ALT and BR elevation did not fulfill strict criteria for a Hy's law case. For instance, patient 301/205-006, summarized below.

301/ 205-006	ALT & AST increased 3xULN after 16 doses of DAC 150, Day 420. Patient was taking paracetamol. Paracetamol stopped on Day 443; ALT normal by Day 466. ALT and AST increased again. On Day 527 ALT was 1.4xULN. Last dose (#21) was given on Day 561. ALT peaked on Day 583 (50x ULN) with AST 20xULN, Total BR 1.5xULN (10x from baseline) and Direct BR 2.14x ULN ; mild elevation of ALP. No concomitant hepatotoxic meds at the time. ANA positive 1:80; liver autoABs negative. Elevated IgE. She received 2 weeks of oral corticosteroids for allergic dermatitis. All AEs were categorized as non-SAE. AST elevation (but
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no ALT elevation) led to drug withdrawal. IFN β started for MS on Day 733. ALT decreased to 2xULN by Day 1001 but was not resolved as of the SUR.

Dr. Avigan speculates that this patient may have had underlying AIH which was aggravated because of treatment with DAC HYP and believes that a causal association with the DAC HYP is "Possible" or "Probable."

Most of the SAE and non-SAE leading to drug withdrawal were confounded by use of other hepatotoxic drugs, including use of IV methylprednisolone for MS relapse, and other drugs commonly used in patients with MS such as antiepileptic, APAP, NSAIDs, antidepressants and muscle relaxants. However, a role of DAC HYP in all these cases could not be excluded.

MP has been reported as a potential cause of acute hepatotoxicity. (30)(31) Although a role of MP is possible, the use of IV MP for MS relapse was greater in the non-DAC HYP treatment groups as compared to DAC HYP groups in both controlled trials, therefore, if the use of IV MP were to increase the risk of DILI one would expect to see more cases on placebo or IFN β 1a groups rather than in the DAC HYP treatment group. Similarly, the use of potentially hepatotoxic drugs such as antiepileptic drugs and analgesics seemed to be balanced among groups in study 201 and 301. If something, the use of NSAIDs was higher in the IFN β 1a group.

Of note, there are two major mechanisms of DILI (11). One is intrinsic drug toxicity (it is dose related, e.g. APAP), and the other is immune mediated (e.g. allopurinol or minocycline), although there is some overlap between the two extremes. The type of toxicity presented by daclizumab appears immune-mediated rather than intrinsic. There are two major types of immune-mediated liver toxicity: Immunoallergic and Autoimmune. These mechanisms can also overlap.¹⁸

¹⁸ The following has been summarized from the LiverTox website (<http://livertox.nih.gov>). Mechanisms of DILI: Immunoallergic hepatitis is accompanied by variable combinations of skin rash, fever, lymphadenopathy, facial edema, myalgia, arthralgia, eosinophilia and atypical lymphocytosis. Phenotypically it may show as cholestatic or mixed, but also as pure hepatocellular, enzyme elevation without jaundice or chronic hepatitis. It usually has a short latency and abrupt onset and is most typical of the aromatic anticonvulsants, allopurinol, sulfonamides and fluoroquinolones. The most dramatic forms of immunoallergic hepatitis are often referred to as DRESS syndrome (drug reaction with eosinophilia and systemic symptoms) and may include Stevens Johnson syndrome or toxic epidermal necrosis. Autoimmune hepatitis (AIH) is marked by the presence of autoantibodies (most typically antinuclear antibody and anti liver antibodies such as Smooth muscle antibody) and hyperglobulinemia (mostly IgG) accompanying the liver injury. Drug induced AIH usually has a long latency (months or years), insidious onset and a hepatocellular pattern of serum enzyme elevations. Liver histology in autoimmune forms of drug induced liver injury resembles the pattern seen in spontaneous or idiopathic autoimmune hepatitis. Symptoms and laboratory test abnormalities usually resolve once the medication is stopped. Drugs associated with autoimmune hepatitis include methyl dopa, nitrofurantoin, minocycline, hydralazine and fenofibrate.

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There were at least 7 SAE of autoimmune hepatitis in this application (202/909-001, 301/670-035, 203/506-011, 302/622-103, 303/649-009, 203/508-012 and 202/765-003). AIH was also in the differential diagnosis for patient 301/624-012 (acute hepatic failure in patient taking valproate after skin reaction to carbamazepine) and 301/670-024 (diagnosed as having cholangitis). Additionally, four patients had non-SAE that led to drug withdrawal and are consistent with immune mediated DILI (301/205-006 had AIH as per Dr. Avigan's assessment (this patient also had allergic dermatitis); 301/451-005 had **liver enzyme abnormal**" associated with pustular psoriasis and eosinophilia, 301/541-005, "**hepatitis**" (AE term cryptogenic hepatitis) also had toxic allergic dermatitis, and 301/474-006 had **ALT elevation >5xULN associated with +ASMA titers** (1:40) and eosinophilia (*this patient was apparently withdrawn for administrative reasons*).

The rate of SAE of AIH with DAC HYP is at least 7/2236 (or 5214 PYRs as of the SUR) = 313 per 100,000 population or 134 per 100,000 PYRs. Including the non-serious immune mediated cases of DILI, there are a total of 11 cases of immune mediated hepatitis (0.5% or 211 per 100,000 PYRs). The overall incidence of AIH in the general population is 1-2 per 100,000 per year, and that includes 9% that are estimated to be drug induced (13). As per Dr. Czaja, an expert on the subject, it is often difficult to determine whether drug-induced liver injury is immune mediated or not, and whether autoimmune hepatitis is spontaneous or drug-induced ("autoimmune-like")(7). These two types of AIH (spontaneous and drug induced) overlap clinically. The only way to distinguish them appears to be response to immunosuppressive treatment. Discontinuation of the offending agent is essential. Spontaneous improvement after stopping drug may ensue. "Corticosteroid treatment is warranted for symptomatic severe disease and it is almost invariably effective"(7). "Relapse after corticosteroid withdrawal probably does not occur and its absence distinguishes drug induced disease from classical autoimmune hepatitis" (7). In order to determine that a case of AIH is fully resolved, the patient should have normal liver enzymes off immunosuppression for at least 3 years (18).

The distinction whether some cases are DILI or AIH and whether AIH is spontaneous or drug-induced is particularly difficult in this database. The investigators use the term AIH without specifying whether it is drug induced or spontaneous. Only one of the cases diagnosed as AIH had positive liver related autoantibodies (302/662-103, anti smooth muscle AB 1:40, supporting AIH). Three were associated with rashes (allergic dermatitis, psoriasis) and 2 were associated with eosinophilia, suggesting an immunoallergic phenotype. At the same time, some cases of potential DILI not diagnosed as AIH did have positive liver autoantibodies (e.g. 203/508-013, reported as having infectious mononucleosis but negative IgM had a positive Smooth Muscle Ab. 1:160) or immunoallergic features (e.g. 201/752-018 had ALT 37xULN preceded by skin rash diagnosed as hepatic yersiniosis -without supportive information-). In terms of distinguishing spontaneous from drug induced based on response to therapy, there is no 3-year follow up data off-immunosuppressor in any of the patients in this database. Moreover, because of DAC HYP long lasting PD effects, relapse of AIH after discontinuation of corticosteroids may not necessarily mean that it was not drug induced.

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Of note, AIH has been reported to be occasionally associated with other autoimmune diseases. (22) However, the association of AIH and MS is not common. (20) A published review of 278 patients with AIH identified that 111 (40%) had some additional autoimmune disease. In that publication, other than Primary biliary cirrhosis and Primary sclerosing cholangitis, the most common concurrent disease associated with AIH was autoimmune thyroiditis (28 patients, 10%); only two patients with AIH were identified as having MS ($2/278 = 0.7\%$). As per another publication, the rate of AIH in untreated MS patients is 23.8 per 100,000 PYRs which is greater than the general population without MS but is lower than the rate observed with DAC HYP.

The literature contains isolated case reports of patients with MS in which autoimmune hepatitis was induced or unmasked by immunosuppressors including interferon beta, glatiramer and natalizumab, (23) to (29) but those were mostly reported in the postmarketing setting after several years of market exposure. The incidence of autoimmune hepatitis in the premarketing database of several drugs recently approved for the treatment of MS are shown in the following table, as well as a data mining search of AIH in the Food & Drug Administration Adverse Event Reporting System (FAERS)

Table 57. Autoimmune Hepatitis reports in premarketing database of recently approved MS drugs

MS drug	N AIH	Exposure at time of SUR	PYRs	Incidence
Fingolimod	0	2615	4500	0
Teriflunomide	0	1513	4500	0
Alemtuzumab	0	1400		0
Cladribine	0	899		0
Tecfidera	0	2665		0
PEG IFN	1	1664		0.06% (60 per 100,000)
Daclizumab	7	2236	5200	0.3% (300 per 100,000)

Source: Individual NDA premarketing databases.

Recent reports of AIH in the postmarketing setting led to labeling changes with Rebif (*reporting rate of AIH was 3/100,000 PYRs but postmarketing reporting cannot be directly compared to clinical trial data*).

The search of FAERS done in July 2015 identified 101 reports of AIH with IFNβ1a, 17 with glatiramer, 4 cases of AIH with Gilenya, 4 with dimethyl fumarate and 6 with alemtuzumab (prior to approval of Lemtrada for MS).

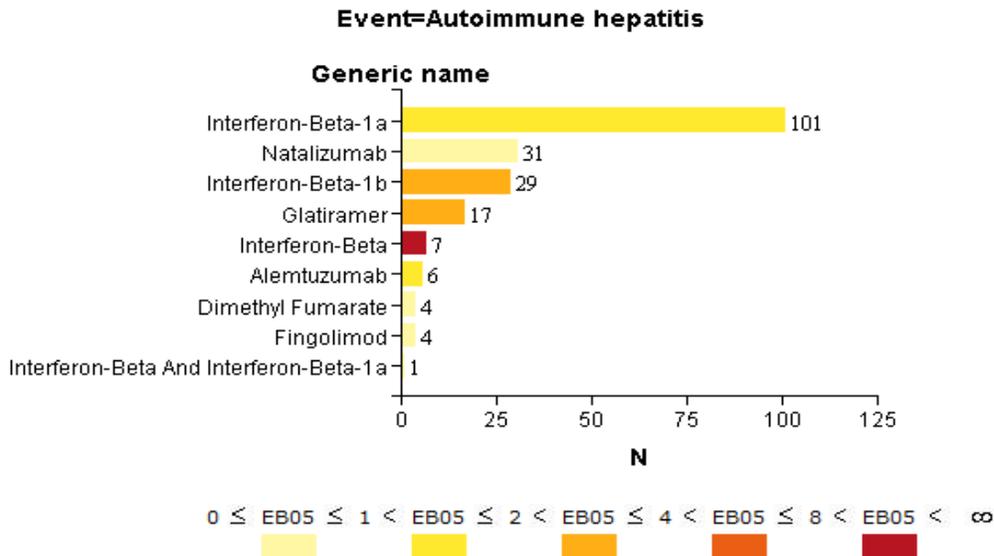
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Figure 10. Data mining search of Autoimmune Hepatitis with MS drugs as of July 2015.



AIH - All MS drugs in FAERS - Empirica Signal. Run by Dr. Villalba July 18, 2015

Data mining search of Autoimmune Hepatitis with MS drugs in FAERS as of 7/18/2015. This may include duplicates.

To provide a rough estimate of patient exposure to various MS drugs, as of February 2015 the exposure to Gilenya (fingolimod) was 237,000 Patient years (source, Gilenya PSUR#8). That would give a rate 2 per 100,000 PYRs. Based on the most recent PSURs, the exposure for Tecfidera (dimethyl fumarate) was 130,000 PYRs, giving a rate of 3 per 100,000 PYRs; and for Tysabri, for the MS and Crohn's indication, there were at least 338,000 PYRs of exposure in patients who received at least 36 doses as of July 2015. That would give a rate of AIH of $31/338,000 = 9$ cases per 100,000 PYRs. I do not have estimates for glatiramer and interferon exposures but these agents have been in the market since 1996 and 1993, respectively and should have substantial PYRs of exposure as well. There have been no reports of AIH with teriflunomide or alemtuzumab during the pre- or postmarketing experience.

Reviewer comment: DAC HYP-induced DILI (whether autoimmune or not), is unpredictable. It can occur at any time during treatment and can be fatal. No particular risk factors have been identified. There are at least 4 Hy's law cases in this application and many other cases of DILI that led to hospitalization and invasive procedures. DAC HYP is obviously hepatotoxic and, in my opinion, clearly more hepatotoxic than IFNβ1a, which already carries a warning for hepatotoxicity. The question is whether the serious risks associated with this product could be minimized by adequate labeling and postmarketing measures – such as a REMS proposed by the applicant - assuming that the product shows adequate efficacy for the proposed indication.

In my opinion, this problem cannot be addressed with labeling and a REMS. First, it would be very difficult to comply with the very stringent eligibility, monthly monitoring and stopping criteria used in these clinical trials in a postmarketing setting, but most importantly, because it

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may not work. Serious toxicity did occur despite strict monitoring and stopping criteria, because the clinical protocol was not followed. If approved, there should be a mechanism that ensures that liver enzymes are drawn and reviewed before the patient gets the next DAC HYP dose. The risk of DILI will be even higher in a wider population using potentially hepatotoxic drugs that were mostly excluded from these trials. Additionally, as discussed in Section 8.3. of this review, the quality of the data submitted in this application does not allow accurate characterization of the liver events (or other toxicities) associated with this drug.

Moreover, it is unclear how many of these cases were drug induced DILI vs. spontaneous AIH. Patients who develop AIH should be followed for at least 3 years after stopping DAC HYP.

As per review of available narratives, at least 8 patients had a liver biopsy and 10 patients were treated with high dose corticosteroids for suspected AIH, including 3 who were also treated with azathioprine.

The potential need for a liver biopsy and/or immunosuppressive treatment needs to be taken into consideration when evaluating the risks and benefits associated with the use of DAC HYP, and if approved, the label should clearly inform patients and physicians how often these kinds of interventions are needed.

8.5.2. Cutaneous Reactions

As of the SUR, 894 (40%) patients had at least one AE in the Skin and Subcutaneous disorders SOC in the Total DAC database, involving a great variety of reactions from mild reactions manageable with topical treatment with or without drug discontinuation to life-threatening reactions or death, despite drug discontinuation, such as in the case of one case of dyshidrotic eczema complicated with bacteremia and psoas abscess 3 months after the drug was stopped for elevated liver enzymes (201/304-006). This patient had received 3 doses of DAC150. Another patient who stopped DAC because of dyshidrotic eczema after 4 doses of DAC150 eventually presented fatal MS relapse with brainstem involvement and aspiration pneumonia/sepsis two months after the last dose of drug.

Cutaneous events occurred at any time during the studies but more often after several months or years of treatment. Of the 894 patients with rash, 13% had a rash that was a SAE, was severe in intensity or led to drug withdrawal.

In study 301, cutaneous reactions were more frequent in the DAC 150 group vs. IFNβ1a for the overall number of AEs (37% vs. 19%) and for several HLT categories, most notably Dermatitis and eczema (14% vs. 6% on DAC 150 and IFNβ1a, respectively), and Rashes, eruptions and exanthemas (10% vs. 4%, respectively). Skin reactions by HLT in study 301 are presented below, for events that occurred in at least 3 patients and with a higher rate on DAC HYP 150.

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Table 58. Skin and SC tissue disorders AE by HLT, Study 301

	DAC HYP 150		IFNβ1a	
	N=	919	N=	922
Any skin and SC AE	343	37.3%	176	19.1%
HLT	n	%	n	%
Acnes	31	3.4%	11	1.2%
Alopecias	16	1.7%	9	1.0%
Angioedema	3	0.3%	0	0.0%
Bullous conditions	3	0.3%	1	0.1%
Dermal and epidermal cond.	38	4.1%	12	1.3%
Dermatitis and eczema	132	14.4%	51	5.5%
Erythemas	32	3.5%	14	1.5%
Exfoliative conditions	20	2.2%	4	0.4%
Papulosquamous conditions	19	2.1%	5	0.5%
Photosensitivity	3	0.3%	1	0.1%
Pruritus	32	3.5%	16	1.7%
Psoriatic conditions	18	2.0%	3	0.3%
Rashes, eruptions and exanthems	88	9.6%	33	3.6%
Rosaceas	11	1.2%	4	0.4%

Source: MedDRA at a Glance analysis conducted by JumpStart team. Only patients with at least 3 events and rate greater than IFNβ1a are included. Additional analyses are shown in Section 13.3.16 of this review). (13.3.16)

Analyses of SAE in the Skin and SC disorders by HLT, for patients with at least 1 event in any treatment group are shown below.

Table 59. Skin and SC tissue disorders Serious AE by HLT, Study 301

	DAC HYP 150		IFNβ1a	
	N=	919	N=	922
Any SAE Skin and SC SOC	14	1.5%	1	0.1%
HLT	n	%	n	%
Angioedema	2	0.2%	0	0.0%
Bullous conditions	3	0.3%	1	0.1%
Hyperkeratosis	1	0.1%	0	0.0%
Dermatitis and eczema	3	0.3%	0	0.0%
Dermatitis ascribed to specific agent	2	0.2%	0	0.0%
Papulosquamous conditions	1	0.1%	0	0.0%
Psoriatic conditions	2	0.2%	0	0.0%
Rashes, eruptions and exanthems	1	0.1%	0	0.0%
Skin cysts and polyps	0	0.0%	1	0.1%
Skin vasculitides	1	0.1%	0	0.0%

Source: MedDRA at a Glance. Analysis conducted by the JumpStart Team.

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As per the tables presented above from study 301, 14 of 343 patients with rashes on DAC 150 (4%) presented a SAE in this SOC, as compared to 1 of 176 of patients with rashes (0.6%) treated with IFNβ1a. (That one patient on IFNβ1a had a dermal cyst). As per table 39 of this review, 5% on DAC 150 had rashes that led to drug withdrawal as compared to 1% of patients on IFNβ1a (whether SAE or not). Therefore, DAC HYP is clearly associated with a greater rate of skin reactions as compared to IFNβ1a, and a greater percentage of those skin reactions becomes a SAE or requires drug withdrawal.

The rate of Skin and SC disorders with DAC HYP 150 and 300 was not very different from placebo in study 201 but this is a small study of only 1 year duration and most skin events tend to occur later.

Of note, the various rashes presented by DAC HYP-treated patients pose a diagnostic challenge to most physicians who are not dermatologists (e.g., differentiating eczema¹⁹ from psoriasis²⁰ and from drug induced eruptions). In fact, the application included a Dermatology Report from (b) (4) the central dermatologist, who is very familiar with DAC HYP's mechanism of action. He tried to use a standardized nomenclature and determine the relationship to study drug for the cases he reviewed. However, the classification and attribution of relationship to study drug was not included in the Dermatology report. As per response to a DNP request for information submitted on July 14, 2015, the information on the dermatologist's assessment of individual cases had not been collected.

The lack of clear nomenclature and attribution of causality by an expert in the field makes more difficult our understanding of the cutaneous toxicity associated with DAC HYP but beyond the ability to adequately classify the events for the purpose of this review, the similarity between these rashes has important clinical implications because the action to be taken with the drug will be different depending on the type or rash. Someone with eczema or psoriasis may not need to discontinue DAC HYP right away but someone with an exanthematous drug eruption should, because it may become life-threatening. Neither the patient nor the neurologist is likely to distinguish among those rashes. Two examples are as follows.

¹⁹ Atopic dermatitis also called eczema is an inflammatory skin disease characterized by skin dryness, erythema, and lichenification with risk of local infection and bacteremia. Symptoms may range from mild pruritus and redness to severe to the point of interference with social interactions and sleep. Mild to moderate disease can be managed with topical steroids and emollients or topical calcineurin inhibitors (e.g. tacrolimus). Acute exacerbations may require short term high-dose systemic corticosteroids. Severe atopic dermatitis may require phototherapy or oral cyclosporine.

²⁰ Psoriasis is an immune mediated inflammatory disease characterized by inflammatory plaques on the skin in genetically susceptible individuals. Defective Treg function has been found in psoriatic plaques. The most common clinical subtype is plaque psoriasis. Psoriasis is associated with multiple comorbidities including arthritis, cardiovascular disease and systemic diseases. Diagnosis sometimes requires a skin biopsy. Patients with moderate to severe disease are usually treated with phototherapy and/or systemic immunosuppressors (biologic and non-biologic) or retinoids.

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Patient 301/115-001 developed non-SAE of postauricular rash diagnosed as seborrheic dermatitis not related to drug on Day 240, after 8 doses of DAC 150; she received two more doses (one on Day 240 and one on Day 258). On Day 277, the patient presented scaly eroded patches on the palms and fingers, followed by exfoliative rash. A skin biopsy showed dyshidrotic eczema that required high dose prednisone and resolved on Day 472 (6 months after last dose of DAC150).

Patient 301/606-019 presented a non-SAE of dermatitis allergic and nummular eczema on Day 419 after 15 doses of DAC150. Events were considered related to drug, but treatment continued. He received 6 more doses. A macular rash was noted on Day 583 (after 21 doses). Event was considered related but received 3 more doses of DAC HYP. Exfoliative dermatitis with cutaneous vasculitis was diagnosed on Day 642 (after a total of 24 doses of DAC150). This event led to drug withdrawal (last dose was on Day 617). Skin rash was treated with methylprednisolone. Vasculitis resolved on Day 647; exfoliative dermatitis resolved on day 923 (9 months after last dose of DAC150).

Upon review of the available narratives, I tried to categorize the skin reactions observed in the DAC HYP program as follows.

- 1) Cutaneous reactions likely related to DAC HYP
- 2) Cutaneous reactions unlikely related to DAC HYP (e.g. skin injuries HLTs; urticaria that resolved without drug discontinuation)

I further classified the reactions likely related to DAC HYP in the Skin and SC tissues SOC into two groups as follows

1. Drug hypersensitivity – Angioedema and urticaria, and Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS), which I will review under, 8.5.3, Immune mediated disorders).
2. Delayed skin reactions – e.g. Dermatitis and eczema, psoriatic conditions, exfoliative conditions, rashes eruptions and exanthemas, bullous conditions and other HLTs.

The categorization I used for review of cutaneous reactions in this application is somewhat arbitrary. Coding of cutaneous events is very complex. The applicant coded all drug eruptions under the Skin and SC disorders SOC. Most cutaneous reactions in this application were reported under the Angioedema and urticaria HLT and the Epidermal and Dermal conditions HLT. Categorization of cutaneous events as per MedDRA 17.0 is shown below, which although not the version used in this applications shows the complexity of this topic.

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- [-] SOC Skin and subcutaneous tissue disorders
 - [+] HL GT Angioedema and urticaria
 - [+] HL GT Cornification and dystrophic skin disorders
 - [+] HL GT Cutaneous neoplasms benign
 - [+] HL GT Epidermal and dermal conditions
 - [+] HL GT Pigmentation disorders
 - [+] HL GT Skin and subcutaneous tissue disorders NEC
 - [+] HL GT Skin and subcutaneous tissue infections and infestations
 - [+] HL GT Skin appendage conditions
 - [+] HL GT Skin neoplasms malignant and unspecified
 - [+] HL GT Skin vascular abnormalities

HLTs under the Epidermal and dermal conditions HLGT are shown below.

- [+] HL GT Epidermal and dermal conditions
 - [+] HLT Bullous conditions
 - [+] HLT Connective tissue disorders
 - [+] HLT Dermal and epidermal conditions NEC
 - [+] HLT Dermatitis and eczema
 - [+] HLT Dermatitis ascribed to specific agent
 - [+] HLT Erythemas
 - [+] HLT Exfoliative conditions
 - [+] HLT Granulomatous and deep cutaneous inflammatory conditions
 - [+] HLT Papulosquamous conditions
 - [+] HLT Photosensitivity and photodermatitis conditions
 - [+] HLT Pruritus NEC
 - [+] HLT Psoriatic conditions
 - [+] HLT Pustular conditions
 - [+] HLT Rashes, eruptions and exanthems NEC
 - [+] HLT Scaly conditions
 - [+] HLT Skin injuries and mechanical dermatoses

The primary SOC for angioedema, drug eruptions and DRESS is the Skin disorders SOC, but the secondary SOC is the Immune system disorders SOC. I chose to review most drug eruptions under the Skin SOC, but angioedema and DRESS along with other immune mediated conditions.

I further categorized the Delayed cutaneous reactions in to 3 groups, as follows

- a) Reactions of T cell dysregulation that would not be unexpected
- b) Drug-induced eruptions
- c) Miscellaneous reactions

a) Skin reactions caused by Tcell dysregulation that would not be unexpected

This group includes Dermatitis/eczema and Psoriasis HLTs. As per (b) (4) Central Dermatologist report:

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“Recent research has established that activated Th2 T-cells are one of the main pathogenic drivers of atopic dermatitis. Hence the mechanistic effects of daclizumab on suppression of Tregs might lead to altered thresholds for activation of skin resident Th2 T-cells and thus (re)activation of eczema.” “Psoriasis is also a common T-cell mediated disease, but is driven by a different effector T-cell subset, Th17.” The “potential action of daclizumab is highly important in considering the range of skin reactions that have occurred in the multiple sclerosis trials, as the skin is normally an immunologic organ, where about 10% of total T-cell immunity is provided by memory-effector T-cells that are resident cells in skin.” “In normal skin, resident T-cells are present in a non-activated state. This state of low immune activity is likely maintained by tolerance mechanisms and active immune suppression by the actions of Tregs. Conversely, if the development or function of Tregs is impaired, spontaneous skin inflammation arises. The overwhelming majority of skin reactions that develop in daclizumab-treated patients are exacerbations of conditions like eczema and psoriasis, where the conditions are believed to be caused by excessive, focal activation of skin-resident T-cells that are "polar" according to the disease.”

*While 40% reported at least one AE in the Skin and SC disorders SOC in the DAC HYP BLA, a recent publication that evaluated the use of DAC HYP in an open label study of 31 patients with MS undergoing dermatologic surveillances showed that **77% of patients developed some type of cutaneous reaction.** (41) As per the authors, the majority presented “with patches of eczema requiring no treatment.” Six (19%) developed moderate to severe rashes and 4 (13%) required discontinuation. “More severe rashes presented psoriasiform phenotype, but lesional biopsies lacked features of either psoriasis or drug hypersensitivity eruptions. Instead, irrespective of clinical severity, lesional biopsies showed nonspecific features of eczematous dermatitis, but with prominent CD561 lymphocytic infiltrates.” “Observed cutaneous AE are likely related to immunomodulatory effects DAC-HYP exerts on innate lymphoid cells, including natural killer cells.” Therefore, **eczema and psoriasis are part of a spectrum of DAC HYP induced cutaneous reactions and should be analyzed together.***

Eczema and psoriasis are not uncommon in the general population, and as noted (b) (4), the rate of these events was within background in the general population. However, analyses in study 301 showed a clear excess of events in patients treated with DAC150 as compared to those treated with IFNβ1a as seen in Tables 59 and 60 of this review.

A total of 337 patients had 539 AE in the Dermatitis and eczema and/or Psoriatic conditions HLTs in the Total DAC HYP database (15%). Of those, 40 had a SAE, a severe AE or an AE leading to drug withdrawal. Mean time to reported serious, severe or event leading to WD was 622 days (median 562, range 74-1974). These patients received a mean number of 24 doses of DAC HYP (median 20, range 3 to 76). However it is unclear how many doses they received prior to the first cutaneous event because some continued receiving treatment before the event became serious/severe or led to WD. Of the 40, 9 did not resolve. For the cases reported as

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resolved, it took a mean of 94 days to resolve (median 83, range 3 to 295 days). It is unclear if the patients were still on treatment at the time of reported resolution.

At least six patients had more than one cutaneous event. 203/353-004 had severe atopic dermatitis on Day 874, that led to drug WD and resolved, but eczema recurred and eventually was a SAE which did not resolve; patient 301/600-004 had contact dermatitis on Day 116, leading to drug WD. Event is reported to end on Day 229, but that day a SAE of pustular psoriasis was reported, that lasted until Day 310. Patient 301/614-027 had severe AE of dermatitis atopic on Day 562 after 20 doses of DAC. Drug was WD and the event resolved on Day 653.

Although eczema and psoriasis are usually non-life-threatening, a substantial number of cases were clinically important. It is unclear how many patients received treatment beyond topical corticosteroids and emollients. As per review of the narratives, at least 5 required systemic corticosteroids (301/512-012, eczematous dermatitis – also treated with plasmapheresis-); 301/600-004 pustular psoriasis; 202/751-011; eczema; 203/115-001, seborrheic dermatitis and exfoliative rash; 301/101-002 -who also needed topical cyclosporine- for psoriasis). Occasionally rashes were associated with alopecia.

It is unclear how many patients with a prior history of eczema and psoriasis were exposed to DAC HYP. In my review of narratives I found at least 2 patients who had mild psoriasis at entry and had exacerbation of psoriasis requiring UV treatment. In an exploratory study of daclizumab Penzberg in patients with psoriasis (DAC-1001), 10% had a psoriatic flare.

In response to an FDA request for information issued on 2/18/16, on 3/8/16 the applicant submitted datasets with information about preexistent history and treatment used for psoriatic conditions in the controlled studies and the total DAC HYP database. At the time of the request it was not clear to this reviewer that eczema is also part of the spectrum of skin reactions associated with DAC HYP, therefore data on eczema was not requested.

As per datasets submitted on 3/8/16, 48 unique patients had a psoriatic reaction in the total DAC HYP database, after 3 to 71 doses of DAC HYP (mean 26, median 24). One fourth of those patients did not receive any further dosing; 75% continued treatment and received 1 to 54 additional doses (mean 12, median 4 doses). Of the 48, 21 resolved and 21 are not recovered/not resolved as of 3/8/16. Of the 48 patients, 9 received systemic corticosteroid treatment (oral, IV and or IM)._

In study 301, psoriasis was presented by 3 patients on DAC150, and 1 on IFN, as follows (data also gathered from Empirica Study).

301/176-006, 29 F presented psoriasis of left hand on Day 54 of DAC HYP after 2 doses of DAC HYP, followed by lesions on both elbows on Day 407 after 15 doses of DAC and worsening

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psoriasis on Day 615 after 22 doses of DAC. No action taken. Treated with topical clobetasol. At the time of psoriasis onset also had blurred vision, pruritus and rash. Later presented lymphadenopathy behind left ear and tenderness left side mastoid tenderness, which did not resolve. She also had left thigh skin nodule that was tender ("possible angiokeratoma). Last dose of DAC HYP was on Day 992. End date for psoriasis was Day 1010, but outcome of psoriasis is Not Resolved.

This patient developed moderate psoriasis after 2 doses of DAC HYP. Drug treatment continued and she was managed with topical steroids. She also had lymphadenopathy, consistent with a DAC HYP induced effect.

301/600-004, 55 M developed palmo-plantar pustular psoriasis on Day 299 to 351, after 6 doses of DAC HYP, treated with balneotherapy and PUVA radiation. Pustular psoriasis was preceded by pustular rash and contact dermatitis, since Day 114 (after 5 doses of DAC), treated with topical clobetasol, betamethasone and 5 day course of prednisone. No action was taken with drug for psoriasis because it had already been withdrawn for contact dermatitis. The last dose of DAC was on Day 140. The event of psoriasis is reported as Not resolved.

This patient developed pustular rash/contact dermatitis after 5 doses of DAC HYP, leading to drug withdrawal after one more dose. Pustular psoriasis developed after patient received systemic prednisone for contact dermatitis. Eventually improved with drug discontinuation and PUVA, but did not resolve. The patient had slightly low thyroxine levels from screening, but thyroid function did not get worse.

301/614-004, 50 M had a prior history of psoriasis for 20 years. At baseline he only had small patches in the lower legs. He presented exacerbation of psoriasis after 12 doses of DAC HYP, but continued treatment and received 41 more doses. He was treated with topical corticosteroids without improvement and hospitalized for 5 days for phototherapy.

Psoriasis on IFN β 1a

Patient 301/459-002. 39F developed guttate psoriasis on Day 999. Event occurred within one month after the last dose of IFN (Day 976). Event was not associated with other immune mediated reactions. Treated with local and systemic corticosteroids (prednisone 25 mg/day) for unclear duration. End date of the event: Day 1168, but outcome was reported as not resolved. *In my opinion this is not related to IFN use.*

Review of cases in study 301 indicates that the same event may have been reported under various PTs (e.g. pustular rash and pustular psoriasis in patient 301/600-004) therefore, the event may have started earlier than the number of doses suggest.

b) Drug induced eruptions

Drug induced skin reactions include a wide spectrum of reactions from mild (e.g. maculopapular or morbiliform eruptions) that resolve with stopping treatment, to life-threatening or fatal such

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as those that fall in the category of Severe Cutaneous Adverse drug Reactions (SCARs). SCARs include Stevens-Johnson syndrome (SJS), toxic epidermic necrolysis (TEN), DRESS and Acute Generalized Exanthematous Pustulosis (AGEP). SCARs require immediate drug discontinuation (33) (41).

There were no cases of SJS or TEN in this application. However, at least 3 patients had a clinical picture consistent with DRESS, and one diagnosed with psoriasis but suspected of AGEP (AGEP)(301/666-007). Cases of DRESS are discussed in section 8.5.3.

I conducted an exploratory analysis just for the Rashes, eruptions and exanthemas HLT, to evaluate whether there was any difference on time to onset and therapy required for these reactions, compared to the eczema and psoriasis reactions. A total of 199 patients had 307 events in this HLT in the Total DAC database. Of those, 30 patients had a SAE, a severe reaction and/or an AE leading to drug withdrawal (15% of all patients with rashes, eruptions and exanthemas, 1.3% of the Total DAC HYP database). Mean day of reported onset was 566 Days (median 452 days, range 1 to 2309). The mean number of doses of DAC HYP received by these patients at the time the event was considered serious, severe or led to WD was 15 (median 13, range 2 to 40).

As per these analyses, Rashes, eruptions and exanthemas tended to occur somewhat earlier than the Dermatitis, eczema and psoriatic rashes (566 vs. 622 days), and after fewer doses of DAC HYP (15 vs. 24 doses), but both tend to present after at least 1 year of treatment, which explain why no major differences were observed between DAC HYP and placebo in study 201, the one-year study. As per datasets, 24 resolved (after a mean of 69 days, median 43, range 3 to 610 days) and 6 did not resolve.

Many skin reactions observed in this application had clinically overlapping features of eczema and/or psoriasis with those of other drug eruptions and exanthemas, exfoliative conditions, papulosquamous conditions, and hyperkeratosis. Some patients presented more than one type of skin reaction concurrently or sequentially (e.g. urticaria and eczema, dermatitis and maculopapular eruptions, etc.). Again it is unclear how many of patients with drug eruptions required treatment beyond topical corticosteroids and emollients, and how long they took to resolve.

c) Miscellaneous drug related Skin Disorders

Some of these disorders are the local manifestation of a systemic immune disease. I classified skin reactions into two groups

- i. Potentially life-threatening reactions if not adequately treated (6 cases of cutaneous vasculitis and one of panniculitis) (they fall into the Vasculitides and Panniculitides HLTs, within the Immune disorders SOC)
- ii. Non-acute skin miscellaneous reactions (fall within the Skin autoimmune disorders NEC HLT, within the Autoimmune disorders HLT, in the Immune disorders SOC).

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i. Potentially life threatening conditions

Reactions such as skin vasculitis and panniculitis require immediate drug discontinuation and starting of aggressive immunosuppressive treatment. There were at least 7 such reactions in this database, as follows.

301/512-011 leukocytoclastic vasculitis (SAE in Skin disorders SOC) with an event on Day 475 that was treated with prednisone and plasmapheresis and resolved).

301/660-008 cutaneous vasculitis (SAE reported under the Vascular system disorders SOC), occurred on Day 245 treated with high dose corticosteroids, on prednisone 15 mg/day as of last follow up; patient later developed erythema multiforme).

301/156-003 (identified in narrative of patient with microscopic colitis, on Day 345, and

301/745-001 (identified in narrative of patient with lichenoid keratosis, on Day 457).

201/751-016, panniculitis was observed in study on day 254 after 9 doses of drug; hospitalized and treated with prednisolone and plasmapheresis.

202/365-002 was reported as Periarteritis Nodosa (PAN). It is unclear if the diagnosis is correct.

303/115-006 A male patient with breast cancer had a preceding/concurrent event of cutaneous vasculitis (*which by the way is not in the datasets*)

Overall, there are at least 5 cases of cutaneous/leukocytoclastic vasculitis and 2 cases of systemic vasculitis (the case of Kawasaki syndrome that I prefer to refer to as ANCA positive vasculitis and the case of Periarteritis nodosa, for which there is very limited information), plus one case of panniculitis treated with plasmapheresis. It is unclear what kind of work-up these patients had to evaluate the events of vasculitis. Usually one would like to see cryoglobulins, complement levels and Hepatitis B testing to evaluate potential etiologies. Of note, the 4 cases of cutaneous vasculitis occurred on DAC150, in study 301. A case of ANCA positive systemic vasculitis also occurred in study 301. No such cases were reported in the IFNβ1a group. The panniculitis occurred in study 201, with no such cases on placebo.

ii. Non-acute skin immunologic reactions- Vitiligo (n=3), cutaneous sarcoidosis (n=1), cutaneous lupus erythematosus (n=1), alopecia areata (n=1).

Most of them were considered non-serious or included very limited information in the narrative. It is unclear if were given any specific treatment. As per a response to an FDA request for information, these cases were diagnosed by dermatologists.

203/453-011 Vitiligo. Received placebo in 201, DAC300 in 202 and DAC150 in 203. Vitiligo was noted on Day 646, on hands and thighs; not considered serious and no action was taken. The event has not resolved. No other AEs. Anti DAC HYP ab positive 1:120 on Day 1717. No other autoimmune labs done.

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303/104-002 Received DAC150 in 301 and 303. Vitiligo Day 1147, non-serious, location unknown. No action taken, event has not resolved. Preceded by livedo reticularis since Day 673 and desquamation of palms on Day 1520. Anti DAC HYP ab negative. No other autoantibodies done.

303/603-003 DAC150 in 301 and 303. Vitiligo Day 818, non serious, face, head, neck trunk, arms, back and penis. Diagnosed by dermatologist as “leukoderma”. Anti DAC HYP ab negative. No autoimmune labs conducted. No action taken with drug; event has not resolved.

Conclusions regarding DAC HYP induced Cutaneous Reactions

Reviewer comment: In summary, DAC HYP was associated with a wide variety of skin reactions. Approximately 37% of all patients exposed to DAC HYP reported an AE in the Skin and SC disorders SOC. These reactions appeared at any time during treatment, with a mean time to onset of 600 days for the most common rashes. As per the datasets, 2% of patients had a SAE in the Skin and subcutaneous SOC, and 5% of all patients discontinued drug because of an event in this SOC. Some rashes required systemic corticosteroid treatment or topical calcineurin inhibitors (7 patients were treated with tacrolimus, including some applied to the face). Most common rashes took a mean of 3 months to resolve after drug discontinuation), but some took several months to resolve and were unresolved at the time of the SUR. Even when reported as resolved, it is unclear how long the patients received local and/or systemic treatment. A small number of cutaneous reactions were life-threatening.

The inability to clinically distinguish early among different rashes is concerning because the treatment approaches are different depending on the type or rash. If approved, patients who develop a rash that does not resolve would need to see a dermatologist before receiving a next dose of DAC HYP. Features that suggest a severe reaction such as DRESS include facial edema, eosinophilia, mucous or conjunctival lesions, painful eyes, skin and epidermal detachment and erosions (41).

Moreover, although not life-threatening, some rashes were aesthetically unappealing (e.g. erythematous, inflammatory, pustular or desquamating rashes) and may have affected the patient’s quality of life.

It is unclear how many of the patients with drug related rashes (eczema, dermatitis, psoriasis, and drug eruptions) had concurrent autoimmune diseases. It would be interesting to evaluate whether the presence of rash correlates in any way (positive or negative) with episodes of MS relapse. The applicant should explore the issue of MS relapse in relationship to skin rashes and other autoimmune diseases.

If DAC HYP is approved, it should be contraindicated in patients with a history of eczema or psoriasis, unless the applicant demonstrates that some patients with such a history tolerated the drug without developing serious rashes.

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8.5.3. Immune mediated reactions

A great variety of immune mediated conditions were observed in this database.

Potential Immune mediated reactions will be presented as follows.

1. Drug Hypersensitivity
2. Immune dysregulation

1. Drug Hypersensitivity

Allergic conditions include events such as hypersensitivity, angioedema and anaphylaxis but also seasonal allergies and reactions to drugs other than DAC HYP (e.g. ibuprofen). I will focus my analyses on cases of angioedema, hypersensitivity and anaphylaxis potentially related to DAC HYP. I am also including the cases of Drug reaction with eosinophilia and systemic symptoms (DRESS) in this section.

a) Angioedema

Angioedema is defined as localized soft tissue swelling that is usually transient. It may be life-threatening if it involves the respiratory airway. Analyses of PT consistent with angioedema (including terms such as allergic edema, angioedema, eye swelling, eyelid edema, face edema, gingival swelling, lip swelling, edema mouth, periorbital edema, swollen tongue) in study 301 showed 22 (2.4%) patients on DAC 150 and 11 (1.2%) on INFb1a. A similar analysis in the Total DAC HYP database identified 80 (3.6%) potential cases of angioedema.

Two SAE and one non-SAE of angioedema leading to drug WD were identified in the database (301/441-021 after 28 doses of DAC150, 301/552-014 (“like Quinke’s edema”) after 34 doses of DAC150 and 202/765-013 after 21 doses of DAC300).

Additionally, there were 3 events consistent with acute hypersensitivity

201/458-007 had an event of “presyncope” on the day of the first dose of DAC300 and rash the day after the first dose leading to drug WD.

203/555-001* was reported as anaphylaxis after 68 doses of DAC150; the patient had been recently diagnosed with sarcoidosis.

303/136-002 was neither serious nor led to drug withdrawal but was severe. Hypersensitivity was reported after 8 doses of DAC150, along with a maculopapular rash that became serious on Day 209, causing drug WD. Not resolved as of the SUR.

As per analyses conducted by this MO using JMP, the rate of angioedema related terms with DAC HYP was 2.5% (23/919) as compared to INFb1a 1.2% (11/922). Listings are included in Appendix 13.3.10 of this review (last page of the section).

Of note, INFb1a carries the following WARNING: “anaphylaxis has been reported as a rare complication of AVONEX use. Other allergic reactions have included dyspnea, orolingual edema, skin rash and urticaria.”

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There were at least 6 cases consistent with acute hypersensitivity reactions (0.3% of the Total database) that were serious, severe or cause drug discontinuation. Acute hypersensitivity may occur at anytime during treatment. These 6 events occurred after 2 to 77 doses of DAC HYP. They were reported to last 1 to 201 days and one is reported as not resolved.

The occurrence of acute hypersensitivity is consistent with known adverse effects of daclizumab Nutley which had Warnings in the Zenapax® labeling. I believe that if this product is approved acute hypersensitivity reactions could be addressed in labeling.

b) Drug Reaction with Eosinophilia and Systemic Symptoms

DRESS also known as Drug Induced Hypersensitivity syndrome (DIHS) or multiorgan hypersensitivity syndrome is characterized by severe systemic disease with fever, rash, lymphadenopathy, and visceral organ involvement (hepatitis, nephritis, carditis, pneumonitis, arthritis, pancreatitis, etc.). Hepatitis is present in 50-60% of cases. Eosinophilia is present in 70-90% of cases. Lymphocytosis with atypical lymphocytes and or monocytosis is sometimes observed. A peculiar feature of the syndrome is its long-lasting clinical course despite withdrawal of the causative drug. There may also be persistent intolerance to other, chemically distinct drugs, leading to flare-up reactions months after the initiating drug therapy is stopped. Drug induced hepatitis, nephritis, interstitial lung disease, pancreatitis or isolated fever can also be the only symptom of a drug allergy. (33)(34). Periorbital and facial edema and erythema with pinheaded-size pustules are the most characteristic cutaneous lesion during the earliest phase of the disease (41). DRESS is caused by various drugs, most commonly antiepileptic, allopurinol, sulfa drugs and antiviral drugs.

The pathogenesis of DRESS has not yet been identified. The clinical picture resembles that of a generalized viral infection, such as an acute EBV infection, but it is distinguished by prominent eosinophilia. **Activated T cells** are often found in the circulation, similar to patients with acute HIV or generalized herpesvirus infections. It has been shown that human herpesvirus-6 DNA (HHV-6) can be found in many patients with this syndrome during the 3rd or 4th week of the disease, but not before, followed by an increase in antibodies to HHV-6. Other reports document reactivation of EBV, CMV and HH-7 infection associated with systemic manifestations and flares of DRESS. It is hypothesized that **drug-induced massive immune stimulation** may somehow lead to a loss of control of these herpesviruses, which subsequently replicate and contribute to the chronic course and persistent drug intolerance. Most expert favor the hypothesis that a simple bystander effect. The significance of virus activation in the pathogenesis of DRESS is unclear.(41) Genetic factors may be important predictors of severe drug reactions.

The cases consistent with DRESS are summarized below

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203/901-006. 39 M. In August 2012, day 336 of study 203, after a total of 26 doses of DAC HYP 150, he was admitted to the hospital with itching of the eyelids, conjunctivitis, bleeding of gums and lips, dry mouth, skin peeling of the lips and weight loss of 10 kg within 3 months, reported as Stevens-Johnson syndrome (SJS). He also had bilateral retinal angiopathy, a WBC of 20,000 x 10⁹/L, with eosinophilia and evidence of tongue edema. Drug was discontinued. He was treated with IV dexamethasone, and electrolytes and discharged with "improved condition". Two weeks later he was readmitted because of increased mucosal ulcers with bleeding of the gums, with tongue swelling, associated with rash on the arms and peeling of the skin on the arms and fingers and swelling of lower legs and enlarged peripheral lymph nodes. A dermatologist thought the clinical picture was consistent with some vitamin deficiency, perhaps Vit B12. Viral testing was consistent with prior infection with HSV 1 and 2 and CMV, but no IgM. ANA was positive. A hematologist diagnosed mild anemia and a neutrophilic leukemoid reaction. The myelogram performed in November 2012 showed blasts 1%, plasmacytes 3%, and binuclear plasma cells. Treatment included IV dexamethasone and oral methylprednisolone. He was discharged with improved condition. The final diagnosis was "**Secondary immunodeficiency with autoimmune syndrome,**" The event resolved on Study Day 478. The subject withdrew from the study. *In my opinion this case is consistent with DRESS.*

The following cases were diagnosed as DRESS by the investigators.

301/512-006 was diagnosed with **DRESS** on Day 213 after a protracted non-serious severe maculopapular rash that started on Day 94, leading to drug withdrawal after 4 doses of DAC. The rash continued to worsen. Labs showed eosinophilia and "slight pancreatitis". The dermatologist noted an erythema multiforme-like rash. Upon diagnosis, patient was treated with prednisolone, antibiotics, fluconazole, and plasmapheresis. It took at least 3 months to resolve. *Although incomplete, the presence of rash, eosinophilia and pancreatitis is suggestive of DRESS.*

303/512-009 **DRESS**, on Days 96-202 after 4 doses of DAC. Patient had highly inflammatory maculopapular rash that led to drug withdrawal. At some point also had lip and face swelling, fever and peripheral eosinophilia (up to 25%, normal range 0-6.8%) and mild ALT increase. Skin bx was read as "toxicodermatitis of an eczematous subacute type with elements of moderate eosinophilia". Treatment included adrenaline and plasmapheresis. Rash improved with plasmapheresis but came back. Patient was started on prednisone 60 mg/day. It resolved but it is unclear how long the patient used prednisone. *Rash, face swelling, fever, eosinophilia, are consistent with DRESS.*

An interesting case observed in this database is that of a patient with CMV infection (201/110-005). This patient presented with a clinical picture consistent with SLE (mouth ulcers, +ANA, ALT>10xULN, weight loss) and also had face edema. A liver biopsy showed CMV viral antigen consistent with CMV hepatitis. The patient was treated with antibiotics, ganciclovir and

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corticosteroids, and the event eventually resolved after recurrent peaks of ALT elevation. *This could be a case of DRESS associated with viral reactivation. This case is an example of the complex relationship between autoimmunity and viral infections.*

2. Diseases of immune dysregulation

In addition to the inflammatory skin conditions (eczema, psoriasis, drug eruptions described under cutaneous reactions), I identified an astonishing number of autoimmune diseases in this clinical program, including “organ specific” (e.g. 27 cases of inflammatory bowel disease [“colitis”]) and systemic immune conditions (e.g. 9 cases of sarcoidosis, 4 of celiac disease).

Immune mediated diseases may be difficult to diagnose and classify because of their overlapping clinical presentation. For instance, Adult onset Still’s disease is a form of RA with an acutely systemic onset that overlaps with a sepsis syndrome and other conditions associated with multiorgan failure. So does hemophagocytic syndrome (HPS). Systemic lupus erythematosus (SLE), sarcoidosis and other rheumatologic diseases may have some of the features of DRESS. Sjogren’s syndrome also has systemic features with predominant lymphadenopathy and salivary gland involvement, usually without the rash. Some of these diseases are typically associated with a set of specific autoantibodies (e.g. +DS DNA, +Smith abs for SLE; SSA and SSB for Sjogren’s syndrome [SS], ANCA for systemic vasculitis). Cutaneous vasculitis may be associated with cryoglobulinemia. Sarcoidosis is not associated with any specific autoantibody. Interstitial lung disease has overlapping features with sarcoidosis. The point is that not only are these diseases complex. Adequate assessment of the extent of the impact of DAC HYP in the immunologic system and the multiple autoimmune or immune-related reactions observed in this program require that 1. The right testing is done 2. That patients be followed long enough to adequately characterize their outcome, including the treatment received (whether corticosteroid or other immunosuppressors were required and for how long) after DAC HYP was discontinued. 3. That the information be collected and conveyed into the narratives and datasets. These conditions were not always fulfilled in this application.

Patients with MS may be at increased risk of developing other immune mediated diseases (32) but analyses in study 301 show an excess of immune reactions in patients treated with DAC150 as compared to IFNβ1a, and indicate that DAC150 increases that risk further.

Of note, in addition to the uncertainty whether some AE are immune related or not because of the lack of complete workup, the total number of patients with reported immune mediated conditions in these clinical studies was difficult to assess because the way these events were coded in the original application (i.e. to different MedDRA SOCs).

In order to identify the total number of patients with immune mediated events I used several approaches. One was to select potential immune mediated conditions flagged by the applicant in the AE datasets. As per this analysis, only 11 (1.2%) had AE on DAC150 and 7 (0.8%) had

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events in study 301. This analysis was missing several preferred terms that should have been included (e.g. sarcoidosis and ulcerative colitis).

On February 18, 2016, DNP asked the applicant to submit datasets for potential immune mediated events (as per a list provided by DNP) with mapping to the primary and secondary SOC (which in most cases was the Immune system disorders). This information was submitted on March 8, 2016. As per these analyses the total number of patients with immune mediated disorders in study 301 **are 170 (18%) vs. 59 (6%)** on DAC HYP and IFNb1a, respectively; and the in the **Total DAC HYP database was 373 (17%)** (data not shown). The list of PTs used for these analyses is included in Appendix 13.3.10 of this review. *Of note, the list included psoriasis but did not include dermatitis and eczema, which in retrospect should have been included given that DAC HYP causes a spectrum of skin rashes that phenotypically may look like eczema or psoriasis but are histologically very similar (47). Moreover, for immune mediated liver toxicity, this list includes only the PT “autoimmune hepatitis.” The list did not include any event potentially associated with MS/MS relapse.*

In addition to the applicant analyses, I conducted analyses including PTs mapped to the Immune system disorders SOC as the primary or secondary SOC in study 301, using the MAED tool with the help of Dr. Vaishali Popat, OCS, and using Empirica Study, with the help of Dr. Ana Szarfman (DCRP). These analyses capture AE such as psoriasis and ulcerative colitis but do not capture eczema. Results are summarized below.

Table 60. Analyses of immune mediated adverse events using mapping to the Primary SOC only or the Primary and Secondary SOCs, in study 301

	DAC150 (N=919)		IFNb1a (N=922)	
	n	%	n	%
By Primary SOC only	28	3	20	2
By Primary and Secondary SOC	163	18	98	11

Source: FDA MO analysis using MAED. May 2015 AE datasets.

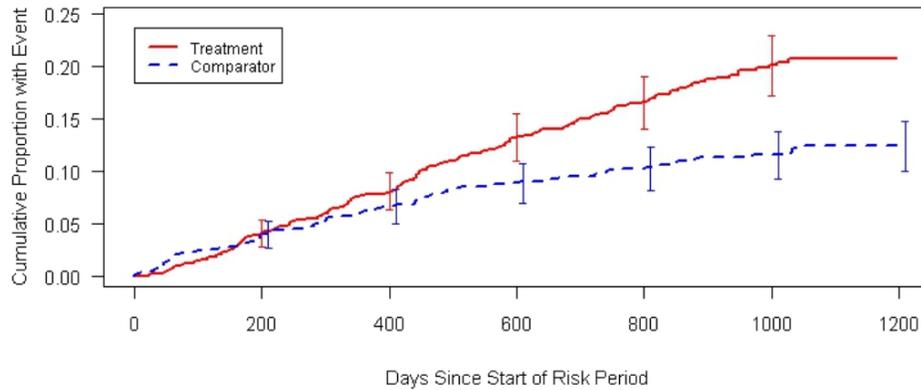
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Figure 11. Cumulative incidence of Events mapped to the Immune System Disorders SOC as primary or secondary SOC.



Subjects At Risk						
Treatment: 919	873	773	675	607	278	0
Comparator: 922	869	760	671	622	357	1

FDA MO analysis using Empirica Study. May 2015 AE datasets.

The analyses by primary and secondary SOC done by either MAED or Empirica Study show a higher rate of events with DAC HYP as compared to INFb1a (**18% vs. 11%**). The curves start to separate after one year, and the difference becomes statistically significant after 600 days.

A third approach was to generate a customized MedDRA Query based on PTs consistent with immune mediated conditions. The customized MedDRA Query was generated with help of Dr. Alan Shapiro, OCS, and included events of eczema, drug eruptions and hypersensitivity/angioedema. The rate of immune mediated events using this approach in the Total DAC HYP database was xx. In study 301, the rate of these events was **32% on DAC HYP vs 12% on INFb1a**. Findings from study 301 are summarized below.

Potentially immune mediated events in study 301 using customized MedDRA Query.

DAC 150 (N=919)			INFb1a (N=922)		
Events	Patients	%	Events	Patients	%
504	295	32.1	158	109	11.8

MO analysis using MAED. Customized Query generated with support from Dr. Alan Shapiro from the Office of Computational Science, run 3/14/16. List is included in Appendix 13.3.10 of this review. PTs potentially related to MS/MS relapse were excluded, and misses cases of immune mediated hepatitis identified by the FDA reviewers.

Selected issues are discussed below

NON-INFECTIOUS COLITIS or ENTEROPATHY

As of the SUR, the Total DAC database included **27 patients** with serious and non-serious AE of “colitis” in the GI SOC, consistent with immune mediated bowel inflammation, including terms

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of Ulcerative colitis (UC), Crohn's disease, inflammatory bowel disease, microscopic colitis, colitis and proctitis. These events are listed in Appendix of this review (13.3.9). Cases of colitis were diagnosed in 21 female, 6 male, ages 19 to 53, with a time to diagnosis of 89 to 1674 days (mean and median around 800 days). Sometimes diagnosis was made a few weeks or months after initiation of symptoms (e.g. bloody diarrhea for months before a specific diagnosis). Of the 27 patients, three occurred on DAC300 and 24 on DAC150 (although 4 had been on DAC300 in the base study). Twelve of the 27, 12 had serious AEs (6 ulcerative, 2 Crohn's disease, 2 colitis, 1 colitis microscopic, one enterocolitis hemorrhagic). One more case of Crohn's disease was reported after the cut-off of the SUR (303/539-010*).

UC and Crohn's disease have typical clinical and endoscopic features, but sometimes are difficult to distinguish from each other. There are some clinical implications regarding the risk of malignancy associated with UC, that is not increased with Crohn's disease, and with other autoimmune processes commonly associated with each of these conditions (e.g. primary biliary cirrhosis for UC; sclerosing cholangitis for Crohn's), but the management is otherwise somewhat similar (high dose corticosteroids and sometimes additional immunosuppression with azathioprine). More concerning to me is the difficulty in distinguishing these conditions from microscopic colitis and unspecific colitis or diarrhea without colitis that do not require systemic immunosuppression, and the need for colonoscopies and sigmoidoscopies (occasionally more than once), to get to the right diagnosis. Some of these patients had protracted GI symptoms for months before the diagnosis was made. Many patients continued DAC HYP treatment despite a diagnosis of UC or Crohn's disease, when in my opinion treatment should have been discontinued right away, knowing that stopping treatment may have helped stopping the autoimmune disease. Some patients ended up hospitalized requiring blood transfusions and electrolyte replacement for severe dehydration and bleeding. Several patients were eventually treated with systemic corticosteroids, and some also received azathioprine. As per the SUR datasets, 12 of the 27 patients had more than one episode of colitis. Eleven of the 27 discontinued drug treatment because of colitis (seven patients upon the first episode; four after a second episode). Three patients had at least one more episode after drug discontinuation (202/502-006, 203/505-026 and 203/559-002). As per the datasets, ten patients with colitis were still on the trials at the time of the SUR, despite unresolved events in three of them.

As of the SUR, 14 events of colitis had not resolved including 4 that had led to drug withdrawal. As per a 9/30/15 response, case 303/611-012 (ulcerative colitis) resolved six months after the last dose; 203/505-011 ("colitis") was "stable" but was ongoing 3 years after last dose of DAC HYP ; 203/505-526 (ulcerative colitis) was considered resolved, although the end date for the

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event was not known; 201/454-007 did not resolve. Even for “resolved” cases, it is unclear if the patient still required treatment for inflammatory bowel disease.²¹

Some of the events of colitis occurred in patients who had non-colitis immune disorders, including skin rashes (allergic dermatitis, erythema nodosum, and vasculitic rash), elevated liver enzymes, pancreatitis, thrombocytopenia and arthritis. At least one of these patients was reported to have hyperglycemia (actual glucose values are not available). UC and Crohn’s disease may be associated with non-GI events but coexistence of several autoimmune processes including eczematoid rashes, autoimmune endocrinopathy and autoimmune enteropathy also resembles an “IPEX-like” syndrome related to defects on the FOXP3 transcription factor and disrupted T cell function. In fact, **the GI expert who evaluated these cases concluded that the cases were not consistent with either UC or Crohn’s but constitute a “distinct DAC HYP associated enteropathy.”**

The cases of colitis for which we have narratives in this application, do not appear to be associated with any particular syndrome, although some of the cases of colitis were reported in patients who also had skin rashes. One case of Crohn’s was reported in a patient with autoimmune hepatitis. *There does not seem to be consistent association with skin rashes or endocrinopathies (thyroid, hypophyseal, type I diabetes), but again, glucose was not measured in the phase 2 and 3 trials and some case of glucose intolerance could have been missed. Analyses of cases of enteropathy using a wide PT as per the applicant’s 3/8/16 submission are discussed in Appendix 13.3.10 of this review.*

CELIAC DISEASE

Celiac disease a chronic immune-mediated disorder triggered by the ingestion of gluten that appears in genetically predisposed patients. It can present with various gastrointestinal symptoms (e.g. diarrhea, weight loss, abdominal pain) or non-gastrointestinal abnormalities (e.g. fatigue, abnormal liver function tests, iron deficiency anemia, skin disorders). The disease is usually detected by serologic testing of celiac-specific antibodies and the diagnosis is confirmed by duodenal mucosal biopsies done under gluten-containing diet. Patients with celiac disease have some genetic predisposition to develop other autoimmune diseases such as autoimmune hepatitis, diabetes mellitus, autoimmune thyroid disease, dermatitis, alopecia areata, vitiligo, rheumatoid arthritis, systemic lupus erythematosus, dilated cardiomyopathy,

²¹ The applicant consulted a GI expert [REDACTED] (b) (4). At the time of the consult – cutoff of the original submission- there were 21 cases of “colitis” in the DAC HYP database. Upon review of the narratives and all available information, including results of colonoscopies and biopsies, [REDACTED] (b) (4) concluded that “the colitis seen in the DAC HYP program is study drug related” and “appear to be related to immune reprogramming by DAC HYP.” “These 21 cases represent DAC HYP colitis, a distinct entity in intestinal inflammation.”

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psoriasis, sarcoidosis, immune thrombocytopenic purpura, microscopic colitis and pancreatitis (many of the autoimmune diseases that were observed in this application). Of note, various neurologic disorders have been reported in patients with celiac disease including multiple sclerosis, gluten encephalopathy, peripheral neuropathy, gluten ataxia, sensorineuro hearing loss, epilepsy, cognitive deficiencies (38) and would be difficult to distinguish whether these neurologic symptoms are from celiac disease or symptoms of MS.

There were at least 4 diagnosed cases of celiac disease in this application, 1 SAE and 3 non-SAE that did not have a narrative. There were no cases of celiac disease in study 301. All four cases were in study 303. The patient with the SAE had a multiorgan reaction similar to those observed with a multiorgan hypersensitivity reaction, an IPEX syndrome or with sarcoidosis (303/141-008, a patient who had been originally diagnosed with ulcerative colitis and also presented hepatitis diagnosed as celiac hepatitis).

SARCOIDOSIS

Sarcoidosis is a systemic immune mediated disease of unknown etiology characterized by the presence of granulomas in involved organs (most commonly lymph nodes and/or lung, [90% of patients] but any organ may be involved including skin, CNS, heart, liver, pancreas, etc.).²² Studies suggest that environmental factors contribute to development of the disease in subjects with genetic susceptibility. Immunologically, sarcoidosis is an exaggerated immune response to so far unidentified antigens. (44)

The prognosis of sarcoidosis varies from a benign course that resolves spontaneously to severe disease with organ damage that requires early treatment with corticosteroids and other immunosuppressors (e.g. pulmonary fibrosis, blindness).(5) Diagnosis may be made based on clinical presentation but the definitive diagnosis may require invasive procedures including mediastinoscopy and lung biopsy, with presence of non-caseating granulomas on biopsy. The incidence of sarcoidosis is 1·0–35·5 in 100 000 per year. The highest rates are reported in northern European and African–American individuals (44).

There were at least 9 patients with a diagnosis of sarcoidosis in the application, including 3 with pulmonary sarcoidosis, plus several cases very suggestive of sarcoidosis (at least 4, in addition to the cases of interstitial lung disease some of which could also be sarcoidosis). Six of the 9 cases diagnosed as sarcoidosis were reported after the cutoff of the SUR, suggesting that they may need longer exposure, they may involve a mechanism that is different from that of colitis, or perhaps it is just more difficult to diagnose. The applicant disputes one of the cases of

²² Sarcoidosis is coded under the MedDRA Immune Mediated Disorders SOC, Immune disorders NEC HLGT, Acute and Chronic sarcoidosis HLT. Cardiac, cerebral, cutaneous, liver, muscular, ocular, pulmonary sarcoidosis are coded to the respective SOC as a primary SOC (e.g cardiac sarcoidosis to the Cardiac disorders SOC), and to the Immune System disorders as secondary SOC.

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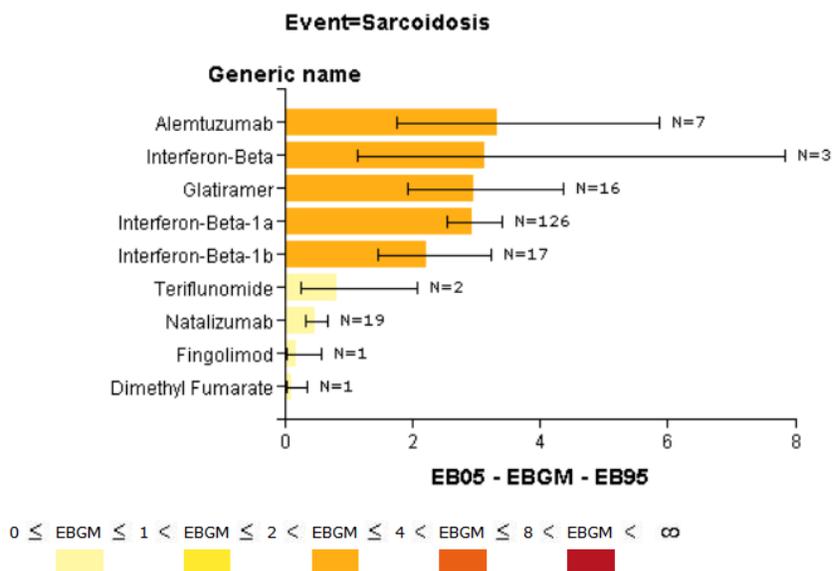
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sarcoidosis. If one takes into consideration only 8 cases, the rate in the Total DAC HYP database is $8/2236=358$ cases per 100,000 patients or $8/5214=153$ per 100,000 PYRs, which is still above the background rate in the general population.

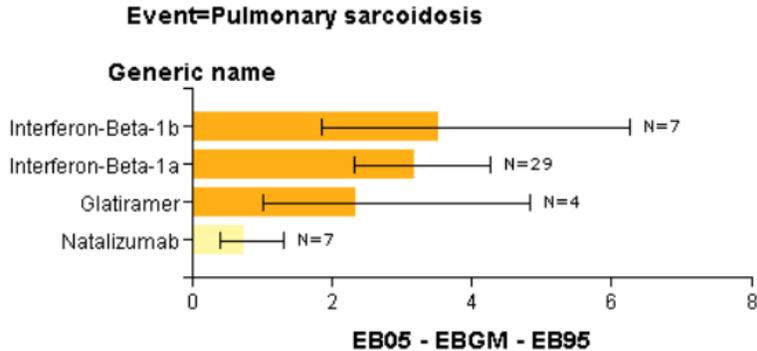
There is no definitive laboratory test for sarcoidosis. Angiotensin converting enzyme (ACE) levels are often increased in patients with sarcoidosis, but they are not reliable for diagnosis or follow up. Calcium is often elevated in patients with sarcoidosis because granulomas produce vitamin D. Neither ACE nor calcium was measured/reported in this database. ACE is not a routine test, but calcium is routine test that is part of any routine chem profile and it should have been obtained in patients suspected of sarcoidosis. Perhaps this could have been used as an early marker although it does not provide a definitive diagnosis.

Of interest, sarcoidosis is characterized by T cell activation. Activated T cells express CD25 and release soluble IL2 receptor (sIL2R). The specific role of sIL2R in the immune response is not completely understood, but sIL2R levels in blood and bronchioalveolar lavage are being used as markers of disease activity in pulmonary and ocular sarcoidosis (6). Patient treated with DAC HYP have increased IL2 levels. The applicant states that this increase is caused by displacement of IL2 from the IL2 receptor. However, it is unclear to me whether it is possible to be sure that IL2 levels are not coming from granulomatous tissue.

Reporting rate of sarcoidosis and pulmonary sarcoidosis with other drugs for MS in FAERS as of February 2016 is shown below.



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Empirica Signal. Run by Dr. Villalba February 5, 2016

As noted above, other drugs approved for the treatment of MS also have some reports of sarcoidosis and pulmonary sarcoidosis, particularly INFb1a and glatiramer. But these numbers accumulated after hundreds of thousand years of patient exposure. Based on the exposure to fingolimod in the most recent PSUR, the rate of sarcoidosis with fingolimod is approximately 1/200,000 PYRs = 5 per million PYRs); similarly, as per exposure provided by Dr. Boehm, the reporting rate of sarcoidosis with Dimethyl fumarate is 1/130,000 PYRs = 8 per million PYRs.

Postmarketing data suggest that sarcoidosis may be associated with other drugs used to treat MS, but the number of cases of sarcoidosis in this BLA is unprecedented for a premarketing database of any drug approved for MS.

The applicant sustains that the risk of sarcoidosis among patients with MS is 4 fold that of patients without MS. However, Dr. Braver (OSE/DEPI) review of the epidemiologic study submitted by Biogen Idec indicates that the findings are inconclusive because of flawed methodology.(45) Main limitations include the lack of adjustment by duration of follow up (patients with MS were followed for longer period than patients without MS); race (the rate of sarcoidosis is greater in the African American population) and the apparent inclusion of patients with preexistent MS.

Discussion and conclusions regarding immune mediated reactions with DAC HYP

Patients with MS are at increased risk of developing other autoimmune disorders. Common predisposing genetic factors have been identified for MS, inflammatory bowel disease, celiac disease and type 1 diabetes mellitus (chromosome region 4q26, related to IL2/IL21, T cell trophic growth factors) and for MS and T1DM (chromosome 10p15, IL2RA alpha chain) (46). Moreover, autoimmune reactions are known to occur in patients using monoclonal antibodies for indications such as rheumatoid arthritis (e.g. tocilizumab [Actemra®]), multiple sclerosis (alemtuzumab [Lemtrada®]) and refractory cancer (e.g. ipilimumab [Yervoy®]). However, the number and variety of autoimmune diseases in this application is unusual for a premarketing database of a monoclonal antibody for an indication other than cancer.

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There is biological plausibility for an increase rate of autoimmunity with DAC HYP. DAC HYP binds CD25 causing downregulation of the CD25 receptor, a decrease in Tregs and increase in NK cells. CD25, IL2RA and FOXP3 transcription deficiencies have been associated with autoimmunity and lymphoproliferation.(1)(2)(3)(42)(43).

Using the customized MedDRA Query, the FDA identified a total of 691 (26.6%) patients with potential immune mediated reactions in the total DAC HYP database. These included 305 patients with dermatitis/eczema (13.6%) 137 (6%) with lymphadenopathy, 48 (2%) with psoriasis, 28 (1.2%) with enteropathy (1.2%), 11 with of immune mediated hepatitis (7 SAE and 4 non-SAE)(0.5%), 9 with sarcoidosis (0.3%), 7 (0.3%) with either cutaneous or systemic vasculitis, 4 of celiac disease (0.2%), and 4 of immune thrombocytopenia, to include only those observed in at least 4 subjects. As per datasets submitted by Biogen on 3/8/16 (which exclude eczema and other rashes), **373 patients (17%)** presented at least one potentially immune mediated event in the total DAC HYP database. 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 have not resolved as of March 3, 2016 (174/373 = **47% of all immune mediated reactions**).

DAC HYP was associated with an increased risk of immune-mediated conditions as compared to IFNβ1a in study 301. IFNβ1a already carries a WARNING for increased autoimmune disorders under 5.7, as follows: “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.”

The rate of immune mediated disorders (with preferred terms mapped to the primary or secondary SOC) in study 301 was 18% vs 11% for DAC150 and IFNβ1a, respectively. As per the 3/14/16 Custom MedDRA Query, the rate of immune-related events in study 301 was **32% vs 12%**. As per the applicant datasets submitted on 3/8/16 (that did not include eczema and other skin related terms), the rate was **18% vs. 6%**. At least 13 patients with events on DAC150 (1.4%) underwent invasive diagnostic or treatment procedures in the DAC HYP treatment group (lymph node aspiration or biopsy, colonoscopy, skin biopsy, thymectomy, thyroidectomy, plasmapheresis, liver biopsy), as compared to 1 (0.1%) in the IFNβ1a group (thyroid biopsy).

In either way one looks, there is an increased rate of immune mediated disorders with DAC HYP as compared to IFN. The applicant acknowledges the increase of cutaneous reactions, lymphadenopathy and colitis but does not see “clear evidence of a broader drug effect relating to other immune disorders.” However, rash, enteropathy and lymphoproliferation are the typical manifestations of the CD25/Treg deficiency syndromes, while specific organ autoimmunity is less common.

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Some of the immune reactions observed in the DAC HYP database are as devastating as MS and may require hospitalization, invasive procedures for diagnosis and/or systemic immunosuppressive treatment, all of which are likely to undermine the quality of life of patients with MS.

I recommend that the issue of autoimmunity be discussed at an Advisory Committee meeting that includes experts in the fields of Allergy and Immunology, Dermatology, Pulmonology, and Risk management/risk communication.

As per discussion with Dr. Amy Rosenberg, a FDA immunologist, it would be important to analyze whether these autoimmune disorders are associated with worsening MS or not, and evaluate whether some of the events characterized as MS relapse are not in fact related to an immunologic effect of DAC HYP on the CNS. Such analyses are beyond this MO's ability and should be requested from the applicant.

8.5.4. Infections

The risk of infections, serious infections and discontinuations because of infections was greater in the DAC HYP groups as compared to placebo and IFNβ1a in controlled trials.

Table 61. Percentage of patients with AE in Infections and Infestations SOC in controlled studies

	Study 201			Study 301	
	DAC150	DAC300	Placebo	DAC150	IFNb1a
	N=207	N=208	N=204	N=919	N=922
All Infections	47.8%	51.4%	42.2%	64.7%	56.7%
SAE infections	2.9%	1.5%	0.0%	4.6%	1.6%
Infections dropouts	0.5%	0.5%	0.0%	0.5%	0.3%

There 3 cases of aspiration pneumonia/sepsis (two of them fatal) and three urosepsis occurred in this database. Additionally one septicemia with Hemophagocytic syndrome and catastrophic antiphospholipid antibody syndrome and one of Kawasaki syndrome with multiorgan failure, treated as if the patient had a bacterial/viral and fungal infection (discussed under multiorgan failure of unknown origin) occurred in this database, but there was no source of infection was identified. Two other patients presented a sepsis syndrome without origin and improved after corticosteroid treatment. It is unclear if these are infections or immune-mediated events.

Opportunistic infections: There were at least 4 cases of TB, and one each of CMV infection, Hepatitis B and C, and 2 infectious mononucleosis (it is unclear if these are true active infections). The case of CMV infection appeared consistent with SLE or malignancy but the patient had a liver biopsy that was consistent with CMV hepatitis. In addition to ALT>10xULN,

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she had mouth ulcers, facial swelling, positive ANA, and weight loss. She was treated with IV methylprednisolone, ganciclovir, antibiotics and chloroquine. The event improved but the patient was lost to follow up. This case is also consistent with DRESS.

CMV infection was identified and a few more cases, including one autoimmune hepatitis who had +IgM for CMV serology with negative PCR (302/662-103); one of the patients with aspiration pneumonia who was found to have CMV in BAL; one patient with lymphadenopathy was thought to have a CMV infection, despite negative IgMab testing (203/205-004*); one patient diagnosed with hypersensitivity pneumonitis also had a diagnosis of "CMV infection of high degree" although it is unclear how the diagnosis was made (301/552-014).

In response to a request for information submitted on 3/3/16, the applicant clarified that patients with active Hepatitis B and C infections were excluded from the studies, but 87 patients with prior Hep B infections (core Ab positive but surface Ag negative) and 6 patients with positive Hep C antibody but negative RNA were included in the DAC HYP studies. Three subjects developed Hep B or C during the studies. None of them had serological evidence of reactivation, and the hepatitis infections appeared to be newly acquired. These cases were 202/106-001, hepatitis C; 203/506-012, Hepatitis C in patient with ulcerative colitis [sigmoidoscopy and biopsy was considered a risk factor for Hep C]; and 201/763-005 acute viral hepatitis B [her husband has same diagnosis].

In regards to CMV infections, CMV testing was included as part of a comprehensive hepatic panel in Study 301 for only those subjects who permanently discontinued dosing due to elevated liver function tests but not included at screening. Therefore, de novo infection vs. reactivation cannot be distinguished.

In regards to the diagnoses of infectious mononucleosis, the applicant stated that the presence of a negative EBV IgM makes the diagnosis of infectious mononucleosis less likely, but cannot rule out other viral causes. It is not possible to rule in or out any contribution of DAC HYP to the event.

Fungal infections

In study 301, 55/919 (6%) vs. 47/922 (5.1%) had an event in the Fungal infections disorders HLG. Only one was a SAE (patient 301/606-020, with systemic vasculitis and sepsis-like syndrome). None led to drug withdrawal. In the total DAC HYP database, 118 patients (5.3%) had an event in this HLG. Of those only one was serious (the patient in study 301 mentioned above) and none led to drug withdrawal.

There is no evidence that DAC HYP increases the risk of opportunistic infections. However lack of evidence is not evidence of absence.

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8.5.5. Malignancies

Please see discussion under Serious Adverse events under Neoplasm.

8.5.6. Neurologic events other than MS relapse

This application included multiple sclerosis as an adverse event. In study 301 all events suspected of MS relapse were reported as AEs. In study 201 it was left at the investigator's discretion. Patients with suspected MS relapse were evaluated by an independent neurologist who was blinded to treatment.

Of note, events not reported as MS included preferred terms such as dizziness, headache, balance disorder, dysgeusia, nystagmus, muscle spasticity, paresthesia. In reviewing the narratives of those events not categorized as MS that were serious or led to drug withdrawal I was not able to distinguish whether they are part of the underlying disease or DAC HYP related AEs. A summary of analyses from the Nervous System disorders SOC is shown below.

Table 62. Percentage of patients with AE in Nervous system disorders SOC

	Study 201			Study 301		Total DAC HYP
	DAC150	DAC300	Placebo	DAC150	IFNβ1a	150 & 300
	N=207	N=208	N=204	N=919	N=922	N=2236
All Nervous S	37.2	35.1	49.0	54.2	63.2	46.6
Nervous S except MS*	19.3	19.7	17.6	36.6	34.3	28.0
SAE Nervous S except MS*	0.5	1.4	0.5	1.5	0.9	1.4
Nervous S except MS* dropouts	0.0	1.0	0.0	0.2	0.3	0.4
Seizures HLG	0.5	0.0	0.5	1.2	0.3	0.8
SAE Seizures	0.0	0.0	0.5	0.7	0.2	0.4

All AEs generated with Empirica Study. AE except MS and AE in total DAC HYP calculated by MO using JUMP. MS includes the following PTs: multiple sclerosis, multiple sclerosis relapse, relapsing multiple sclerosis and progressive multiple sclerosis.

When including all AE in the Nervous system disorders SOC, there was a clear excess of events in the placebo or INF groups as compared to DAC HYP treatment in the controlled trials. However, for events other than MS relapse, there a slightly higher percentage of patients with AEs in the DAC HYP treatment groups as compared to placebo and IFN β1a (1-2% difference). There was no difference in the rate of AE that were serious or led to drug withdrawal between treatment groups. This review does not include evaluation of cases reported as MS.

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There was a higher risk of seizures in the DAC150 treatment group as compared to INFβ1a (11 [1.2%] vs 3 [0.3]) in study 301.

Non-clinical studies identified microglial aggregates in the brain of monkeys treated with DAC HYP. DAC HYP is associated with increased serum and intrathecal IL-2 levels in humans (as per page 34 of the summary of non-clinical safety). The applicant hypothesizes that microglial aggregates in monkeys may be a consequence of increased IL-2 levels (although IL-2 levels were not measured in monkeys). The applicant acknowledges that “overactive microglia have been associated with deleterious effects relating to neurotoxicity and neurodegenerative diseases and neuroinflammation,” and that “microglial nodules have been reported in the normal-appearing white matter in MS patients associated with axonal degeneration.” It is unclear to me whether microglial aggregates –if they were present in humans- could be recognized in an MRI and distinguished from MS lesions.

Biologic agents are known to induce neurologic autoimmune diseases such as Guillain-Barre, optic neuritis, demyelinating CNS disease, encephalitis, aseptic meningitis, peripheral neuropathies, chronic demyelinating inflammatory polyneuropathy (CDIP) and multiple sclerosis(23). In fact, there were autoimmune disorders in other organ systems in this database (e.g. 28 cases of colitis, 7 of autoimmune hepatitis). Therefore, it is conceivable that DAC HYP could increase the risk of autoimmune neurologic conditions too.

Two fatal cases of aspiration pneumonia and sepsis occurred in patients who had neurologic AE that could potentially be caused by DAC HYP. The cases are summarized below.

- 301/431-004 37 F. received 3 doses of DAC HYP. Three weeks after the last dose she developed palmoplantar dyshidrotic eczema and sialadenitis of the mouth. Events worsened. No further doses were given. Two months after the last dose of DAC, she had a severe MS relapse with possible brainstem involvement (that she did not have before receiving DAC) complicated with aspiration pneumonia, sepsis, shock and fatal multiorgan failure.
- 301/744-007 received 4 doses of DAC HYP. Ten days after the last dose she presented “acute exacerbation of MS involving the brainstem, “not a relapse” and aspiration pneumonia. MRI showed extensive increased white matter lesions bilaterally and increased cerebral demyelination. She was immediately treated with azathioprine, which suggest this “not a relapse” was very different from any prior MS relapses the patient had. The event of MS relapse resolved but the event of aspiration pneumonia was ongoing. She died of complications of aspiration pneumonia 3 months after the last dose of DAC HYP.

A third patient with aspiration pneumonia was reported in a patient with “tumor-like demyelination” (a “non-protocol defined MS relapse”) after 43 doses of DAC HYP (303/611-015). The patient was treated with IFNβ1a as alternative MS therapy. Three months after the

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last dose of DAC HYP he had aspiration pneumonia, respiratory failure and septic shock. He was treated in the ICU, had a tracheostomy and started MS treatment with natalizumab.

There were at least three additional events consistent with an immune related reaction in this SOC, as follows.

- 303/600-010. Myasthenia gravis in a patient who was diagnosed with thymoma. The event started in study 301 and was diagnosed while in 303. He underwent thymectomy. He also had evidence of peripheral motor neuropathy, with atrophy of small muscles of the right upper and lower extremities. The event is reported as not resolved. Pathology results from the thymus are still pending.
- 202/363-008. Aseptic meningitis occurred in association with a maculopapular rash, approximately 1 ½ months after the last dose of DAC in study 201. Infectious disease workup was negative. The patient was treated with empirical antibiotic and antiviral treatment. The event of meningitis is reported as resolved after approximately 2 weeks. AntiDAC antibody testing was positive. Neutralizing AB was transiently positive.
- 303/659-001, diagnosed with cerebral venous thrombosis and had recently been diagnosed with sarcoidosis.

Additionally, patient 202/509-014 was diagnosed with demyelination / central pontine myelinolysis. There is not definitive evidence to support such diagnosis.

This medical officer—who is not a neurologist—cannot distinguish whether neurologic AE reported as “not MS relapse” in this application (e.g. demyelinating disease, seizure, peripheral neuropathy) are part of the underlying disease or a DAC HYP induced adverse reaction. *Dr. Rodichok, primary reviewer for the efficacy part of the application will comment on these cases.*

8.6. Specific Safety Studies/Clinical Trials

No specific safety studies were conducted.

8.7. Additional Safety Explorations

8.7.1. Human Carcinogenicity or Tumor Development

Please see section on breast cancer and lymphoma under SAE of Neoplasms.

8.7.2. Human Reproduction and Pregnancy

As of March 2014 there were 9 on DAC HYP, after 4 to 43 doses. Of the nine, 8 stopped drug once they were aware of the pregnancy; for one case, action taken with drug is unknown. Diagnoses were made by protocol mandated pregnancy tests, confirmed by ultrasound. Fetuses

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were exposed for 1 or 2 doses. Five of the nine had live births with no obvious congenital malformations; three were lost to follow up or outcome is not available; one had an early termination. The list of pregnancies on DAC HYP as of March 9, 2015 is presented in Appendix 13.3 of this review (13.3.14)

8.7.3. Pediatrics and Assessment of Effects on Growth

Not applicable

8.7.4. Overdose, Drug Abuse Potential, Withdrawal, and Rebound

Based on the mechanism of action and safety profile of DAC HYP, the lack of signal for abuse or dependence properties in nonclinical and clinical studies of DAC HYP as well as other anti-CD25 agents, the applicant concluded that DAC HYP has a low potential for abuse and does not require scheduling as a controlled substance. At the pre-BLA meeting the CSS agreed that there is no need to conduct a study for assessment of abuse potential.

8.8. Safety in the Postmarket Setting

8.8.1. Safety Concerns Identified Through Postmarket Experience

Not applicable for DAC HYP.

Postmarketing data exist from two marketed anti-CD25 MoAbs: Daclizumab Nutley (Zenapax) and basilixumab (Simulect). The labeling for Zenapax (which was withdrawn from the market because of a business decision, not because of specific safety issues) mentions immediate hypersensitivity reactions but does not mention autoimmune diseases. Evaluation of postmarketing reports in FDA FAERS did not identify cases of AIH with DAC Nutley but identified two cases of AIH with basilixumab.

The safety of these other anti-CD25 antibodies (presence of absence of serious AEs) does not directly apply to daclizumab HYP because of the different target population (transplant patients, receiving other immunosuppressors, versus patients with MS) and dosing schedules (short term use for treatment induction for DAC Nutley and basilixumab, versus chronic, monthly use for DAC HYP). For additional information see Appendix 13.3 of this review (13.3.19).

8.8.2. Expectations on Safety in the Postmarket Setting

I am very concerned about the ability of physicians and patients to follow the directions in

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labeling regarding the required monitoring for liver toxicity. If approved, I anticipate that serious, life-threatening and fatal events will occur related to liver toxicity. Moreover, DAC HYP is associated with other immune mediated disorders such as colitis, sarcoidosis; pneumonitis, glomerulonephritis, that may be more difficult to identify/monitor than the liver enzymes. Additionally, DAC HYP is associated with a variety of cutaneous reactions, occasionally complicated with local and systemic infection. Some of these heterogeneous reactions are difficult to distinguish clinically with important implications because the need of a different therapeutic approach. Patients in the postmarketing setting will be in a worse clinical condition than patients who participated in these clinical trials. In my opinion this is not a drug to be given to patients with severe chronic disability or a precarious clinical condition that could easily be disrupted by a major organ biopsy or by palmoplantar lesions that interfere with using their hands or with walking. The safety of DAC HYP is not well characterized as to be able to guide patients and physicians on the minimization of serious risks associated with its use.

8.9. Additional Safety Issues From Other Disciplines

All reviews are pending at the time of this review, except the consultations from Drs. Senior and Avigan, regarding liver safety. A summary of their assessment is included in Appendix 13.3 of this review (13.3.6].

8.10. Integrated Assessment of Safety

Safety findings from this database are summarized below

- The safety database for DAC includes 3 clinical trials in RRMS (1 Phase 2 placebo-controlled study (201), 1 active controlled study (301), one phase 3 open label study (302) and their extensions in adult patients with MS. The number of patients (2236 subjects), length of exposure (5214 PYRs) and characteristics of the population in terms of age and gender are sufficient to evaluate the safety of DAC in the intended population for use. The database contains a small number of patients with races other than White to allow conclusions regarding safety in other races/ethnicities. The proposed dose is 150 mg s.c. every 4 weeks. The percentages of patients with relevant safety findings in the DAC HYP BLA are shown below.

	Study 201			Study 301		Total DAC HYP
	DAC150	DAC300	Placebo	DAC150	IFNb1a	150 &300
	N=207	N=208	N=204	N=919	N=922	N=2236
Deaths ¹	0.5	0.0	0.0	0.2	0.2	0.2
All AE except MS ²	72.0	73.1	68.6	91.3	88.3	81.8
SAE except MS	7.2	8.7	5.9	15.5	9.4	15.7
AE dropouts except MS	2.9	3.8	1.0	14.3	9.0	12.9

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¹ Within 6 months after last dose for DAC HYP; within 1 month after last dose of IFNβ1a. ² Excludes the following PTs: multiple sclerosis, multiple sclerosis relapse, relapsing remitting multiple sclerosis, progressive multiple sclerosis.

Except for MS/MS relapse, the rate of AE, SAE and dropouts because of AE was greater in the DAC HYP group as compared to IFNβ1a.

• Safety Concerns

Deaths: There were five deaths in the DAC HYP clinical program. Two were clearly drug related and DAC HYP may have played a role on the other 3. DAC HYP- related deaths include 1 liver failure secondary to autoimmune hepatitis (AIH) and 1 infectious complication of dyshidrotic eczema, 3 and 2 months after the last dose of DAC HYP, respectively. The other 3 deaths were 2 aspiration pneumonia & sepsis in patients with MS progression [immunosuppression may have favored a negative outcome] and 1 intracranial bleeding after a fall in a patient with lymphoproliferative disorder anticoagulated for DVT [there is very little information about the lymphoproliferative process that could potentially have been related to DAC HYP]). There were 5 deaths among patients treated with IFNβ1a in study 301, 3 of which occurred beyond 1 month after stopping drug. All appeared not to be drug related.

Drug-induced liver injury: SAE of drug induced liver injury (**DILI**) occurred in at least 21 of 2236 DAC-HYP treated subjects in the total DAC database (**0.9%**) including 4 Hy's law cases (0.3%).

Percentages of patients with liver related event/labs in the controlled studies are summarized below.

	Study 201			Study 301	
	DAC150	DAC300	Placebo	DAC150	IFNβ1a
	N=207	N=208	N=204	N=919	N=922
SAE Hepatobiliary*	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 >5xULN	4.3	3.8	1.0	5.8	3.2
ALT >10xULN	3.4	1.4	0.0	2.6	1.2
ALT >20xULN	1.4	1.0	0.0	1.0	0.4
ALT >3xULN, BR>2xULN, ALP<2xULN	0.5	0.5	0.5	0.7	0.1

*Hepatobiliary refers to the Hepatobiliary disorders SOC and Investigations SOC, Hepatobiliary HLG. These SOC include AE of cholecystitis and biliary colic that are not drug induced liver injury.

There were small differences in the percentage of liver related events/labs in the one year

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study. Analyses indicate that DAC HYP is associated with greater hepatotoxicity than IFNβ1a, which already carries a warning for hepatotoxicity.

Most cases of DILI were confounded by concomitant medications that are potentially hepatotoxic, however, the use of potentially hepatotoxic medications was balanced in study 301.

Overall, at least 11 cases of immune mediated hepatitis related to DAC HYP were identified in the Total DAC HYP database (7 were SAE; 4 were non-SAE that led to drug withdrawal, 3 of which were associated with rash). At least 8 patients were treated with high dose corticosteroids including 3 who were also treated with azathioprine. At least 2 were still on corticosteroid treatment >2.5 years after stopping DAC HYP. Ideally patients should be followed for 3 years after stopping immunosuppressive treatment for AIH to determine resolution.

Other than the fatal case, all cases of DILI are reported to have resolved after DAC HYP discontinuation. Precise length to full resolution of liver events is unclear, and at least the two patients with AIH mentioned above should not have been reported as resolved because they are still on treatment.

Cases of DILI occurred despite monthly monitoring of transaminases and BR. Half-way into study 301 all sites were provided the option to use a point-of-care analyzer for monthly LFT (for study 301 and all ongoing studies). Genomics testing did not identify a marker for hepatotoxicity.

Cutaneous reactions: Occurred in 40 % of patients in the Total DAC HYP database. Percentages of patients with cutaneous events in the controlled studies are summarized below.

	Study 201			Study 301	
	DAC150	DAC300	Placebo	DAC150	IFNb1a
	N=207	N=208	N=204	N=919	N=922
All AE in SOC	15.9	18.3	12.7	33.7	17.5
SAE in SOC disorders	1.0	1.4	0.0	1.5	0.1
AE dropouts in SOC	1.4	1.4	0.0	4.7	0.8

There were small differences in the percentage of cutaneous events as compared to placebo in the one year study. Analyses indicate that DAC HYP is associated with greater cutaneous toxicity than IFNβ1a.

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Cutaneous reactions occurred throughout the clinical trial period. Difficulty distinguishing among various rashes that occurred (e.g. eczema, psoriasis, severe cutaneous drug reactions, cutaneous vasculitis, cutaneous sarcoidosis) has important clinical implications because they require different a therapeutic approach and action with DAC HYP.

A small number of patients required hospitalization, administration of topical tacrolimus or systemic corticosteroids, or plasmapheresis. Other than the patient who died of infectious complications of dyshidrotic eczema most cutaneous reactions are reported as resolved. However, time to resolution in some cases required months and in some cases whether the reaction resolved or not was unknown. It is unclear whether any patient with a prior history of psoriasis or eczema who did not develop these types of reactions while treated with DAC HYP. Whether a biomarker could predict any of the skin reactions has not been evaluated.

Immune mediated reactions

Potential Immune mediated adverse reactions occurred in 691 (27%) of patients in the total DAC HYP database (based on a customized MedDRA query). The most common reactions were cutaneous reactions (eczema/dermatitis/ psoriatic conditions) (15%), lymphadenopathy (6%) and enteropathy (1.2%) 12 of whom required hospitalization. Other immune mediated reactions included autoimmune hepatitis, sarcoidosis, celiac disease, interstitial lung disease and immune thrombocytopenia, to list events reported in at least 4 patients. Some events presented concurrently or sequentially in the same patient. For instance, one patient presented rash, drug induced liver injury, pancreatitis and Type 1 diabetes mellitus over a 2 month period. Some reactions required hospitalizations, invasive procedures and biopsies (such as colonoscopy, mediastinoscopy, liver and renal biopsies, in addition to skin and peripheral lymph node biopsies), and prolonged treatment with immunosuppressive therapy such as IV or oral corticosteroids and azathioprine. Approximately half of the potential immune mediated reactions have not resolved as of March 8, 2016.

The rate of immune mediated reactions using the customized MedDRA query approach in study 301 was 32 % on DAC HYP 150 and 12 % on IFNβ1a. As per the datasets submitted on 3/8/16 (which exclude eczema and other rashes), the rate was 18% vs. 6% on DAC150 vs. IFNβ1a, respectively. At least 12/919 patients (1.3%) underwent invasive diagnostic or treatment procedures in the DAC HYP treatment group (lymph node aspiration or biopsy, colonoscopy, skin biopsy, thymectomy, thyroidectomy, plasmapheresis, liver biopsy), as compared to 1/922 (0.1%) in the IFNβ1a group (thyroid biopsy).

The rate of lymphadenopathy/lymphadenitis/lymphoid tissue hyperplasia in study 301 was 5% on DAC150 and 0.8% on IFNβ1a. Most of these cases were not fully worked up, including several cases highly suggestive of sarcoidosis because of the presence of hilar

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lymphadenopathy. Less than 10% of patients with SAE of L/L/L had fine needle aspiration or biopsy. Fine needle aspiration may miss sarcoidosis and lymphoma. Hypercalcemia could have been a potential marker for sarcoidosis, but calcium levels were not measured in the controlled trials.

The onset of immune mediated reactions is unpredictable. The severity of the event and the work up and treatment required depends on the organ system involved. The applicant has not evaluated whether a biomarker can predict patients at risk for immune mediated reactions.

Acute hypersensitivity

At least 6 events of angioedema or anaphylaxis that were serious, severe or led to drug withdrawal occurred in the total DAC HYP database after 2 to 77 doses of DAC HYP. Additional information has been submitted and review is pending at the time of this review.

Multiorgan hypersensitivity

Overall, at least 3 cases in the database were consistent with multiorgan hypersensitivity/drug reaction with eosinophilia and systemic symptoms (DRESS). The syndrome is characterized by fever, rash, lymphadenopathy, facial edema, internal organ involvement (e.g. hepatitis, nephritis) and hematologic abnormalities. Eosinophilia may be present. Although common, rash and eosinophilia do not need to be present to make the diagnosis. Activated T cells are often found in blood of patients with DRESS, similar to patients with generalized herpesvirus infections. Reactivation of Human herpes virus infections such as HHV-6, CMV and EBV infection have been documented in some patients. It is hypothesized that drug-induced massive immune stimulation may somehow lead to a loss of control of these herpesviruses, which subsequently replicate and contribute to the chronic course and persistent drug intolerance. The applicant evaluated cases reported as DRESS but concluded that they did not fulfill the RegiSCAR criteria. I believe that in two of the cases there is limited information to rule out DRESS, moreover, I strongly believe that the cases reported as SJS by the investigator was a case of DRESS, whose final diagnosis was “secondary immunodeficiency with autoimmune syndrome”.

Four patients presented a sepsis-like picture of unknown source in the Total DAC HYP database. These were one case of hemophagocytic syndrome, one of ANCA positive systemic vasculitis, one sepsis/fever of unknown origin and one Still's disease adult onset. In addition to antibiotic, antivirals and in one case, antifungal treatment these patients were treated with high dose systemic corticosteroids and/or plasmapheresis. These 4 sepsis-like cases are consistent with an immune-mediated systemic inflammatory response, with a clinical presentation that is somewhat similar to the cases of DRESS, making 7 cases of multiorgan hypersensitivity.

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Infections: Infections occurred in 48% on DAC 150 and 42% of patients on placebo in study 201 and in 65% in DAC 150 and 57% of IFN β 1a patients in Study 301. SAEs occurred in 2.9% of DAC 150 vs none on placebo in Study 201 and in 4.6% of DAC 150 vs 1.6% IFN β 1a in Study 301.

The most common SAE in this SOC were pneumonia and urinary tract infection. In addition to the fatal infections mentioned above, there was one more case of aspiration pneumonia and sepsis in a patient with worsening MS and 3 of urosepsis.

Opportunistic infections included 4 cases of tuberculosis in patients from countries where TB is endemic. There is limited information on how the diagnoses were made, the current status or outcome. One patient hospitalized with respiratory symptoms and lung interstitial nodules underwent extensive work up including bronchioalveolar lavage and biopsy of hilar lymphadenopathy. All cultures were negative, but the patient was diagnosed as “probably TB” and treated empirically with anti TB and antifungal medication. Additional follow up has been requested for this patient.

Viral infections: CMV infection, hepatitis B and C and infectious mononucleosis were reported in this application. It is unclear if some of these cases are new infections or viral reactivation.

One patient with a SAE of CMV infection had mouth ulcers, ALT>10x ULN, face edema, 20 Lbs weight loss and + ANA among other signs and symptoms. The clinical picture was consistent with systemic lupus erythematosus or lymphoma. A liver biopsy was suggestive of CMV hepatitis. She was treated with IV methylprednisolone, ganciclovir and chloroquine. The event is reported as resolved 5 months after last dose of DAC HYP but the patient was lost to follow up. This event is consistent with DRESS.

As mentioned above, there were at least 4 patients with a sepsis-like systemic inflammatory response of unknown origin (3 of whom were reported under the Infections and infestations SOC), that could be immune mediated events.

Other relevant SAE in the infections SOC included one patient diagnosed with brucellosis with hepatic involvement and one diagnosed with yersiniosis with hepatic involvement. There is no adequate evidence to support either diagnosis.

Neurologic events other than MS relapse

Multiple sclerosis was reported as an adverse event in this application. Percentages of patients with AE in this SOC Excluding preferred terms related to MS are shown below.

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	Study 201			Study 301		Total DAC HYP
	DAC150	DAC300	Placebo	DAC150	IFNβ1a	150 & 300
	N=207	N=208	N=204	N=919	N=922	N=2236
Nervous System except MS*	19.3	19.7	17.6	36.6	34.3	28.0
SAE Nervous S except MS*	0.5	1.4	0.5	1.5	0.9	1.4
Nervous S except MS*dropouts	0.0	1.0	0.0	0.2	0.3	0.4
Seizures HLGT	0.5	0.0	0.5	1.2	0.3	

*MS preferred terms include multiple sclerosis, multiple sclerosis relapse, relapsing multiple sclerosis, progressive multiple sclerosis.

The rate of AE other than MS was slightly (1-2%) higher on DAC HYP as compared to placebo and IFNβ1a, in the controlled studies. The rate of seizures in study 301 was 3-fold higher on DAC HYP as compared to IFNβ1a.

Biologic agents have been reported to induce autoimmune conditions including some in the nervous system. DAC HYP increased the rate of autoimmune disorders as compared to Avonex in study 301 and was associated with a great variety of autoimmune diseases in organs outside the nervous system. There were at least two immune mediated AE in the nervous system SOC (one case of myasthenia gravis and one consistent with aseptic meningitis). In reviewing the narratives of other events not categorized as MS relapse that were serious or led to drug withdrawal (e.g. seizures, “tumor-like demyelination”) I was not able to distinguish whether they are part of the underlying disease or DAC HYP related adverse reactions.

Non-clinical pharmacology studies showed microglial aggregates in the brain of monkeys. It is unclear whether microglial aggregates, if they were to occur in humans, could be distinguished from MS lesions in an MRI.

Malignancies: There were 3 non-Hodgkin’s lymphoma treated with chemotherapy and one suspected lymphoma that is resolving off-drug. 3/5214 PYRs=58 per 100,000 PYRs which is higher than background for ages younger than 65 years (9.3 per 100,000 population per year). At least 9 cases of breast cancer were diagnosed in this database, including one in a male subject (all in extension studies).

Data quality: It is important to emphasize that analyses generated from these datasets under-represent the toxicity associated with DAC HYP. The estimates regarding number of cases with regulatory definition of serious, duration of event and whether patients continued on drug or not, whether they resolved or not and how long they took to resolve are uncertain. Relevant events are missing (e.g. diagnostic procedures for

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evaluation of adverse reactions during DAC HYP). The information on outcomes is incorrect or incomplete (an adverse reaction could be considered resolved while patients were still on treatment for that reaction). As per a response submitted in September 2015, 7% of patients with SAE or AE leading to drug withdrawal had an outcome reported as “unresolved” or “unknown”. Of note, glucose, calcium, uric acid, phosphorus and albumin were not routinely measured in the DAC HYP clinical studies.

I recommend not approving DAC HYP, based on safety concerns, unless the efficacy is overwhelming.

When the FDA approves a drug, it is implicit that “the benefits outweigh the known risks.” DAC HYP induces profound disruption of the immune system consistent with known CD25/Treg deficiency syndromes characterized by uncontrolled autoimmunity. There are currently 12 other drugs to treat MS, in addition to corticosteroids. Patients should be aware that this product might induce serious autoimmune processes (autoimmune hepatitis, inflammatory bowel disease, interstitial lung disease, sarcoidosis), as well as eczematous, psoriatic, exfoliative, bullous and pustular rashes, infections and seizures, while decreasing the rate of MS relapse without showing benefit on progression of disability.

9 Advisory Committee Meeting and Other External Consultations

There was no AC planned for this product. In my opinion, given the very unfavorable safety profile of this drug, if approval is a consideration, an AC should be held before approval. Moreover, I recommend an AC that includes a clinical immunologist, an hepatologist, a dermatologist, a gastroenterologist, and an expert on Tcell regulation.

10 Labeling Recommendations

I recommend not approval of this product based on safety concerns. However, if approved, the label should include a boxed warning for DILI, cutaneous reactions and autoimmunity.

11 Risk Evaluation and Mitigation Strategies (REMS)

I recommend not approval of this drug, based on safety concerns. As per a meeting held on 3/7/16, if approved, this product should have a REMS with ETASU. A REMS may mitigate some of the serious risks associated with DAC HYP but it will not eliminate them.

11.1. Safety Issue(s) that Warrant Consideration of a REMS

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-Major concerns with this biologic agent are the drug induced immune related reactions including cutaneous, liver and other organ systems.

In the clinical trials, DAC was administered by health care professionals. In the postmarket setting, the sponsor plans for patient self-administration, without the benefit of a healthcare professional evaluating laboratory work or clinical signs and symptoms of adverse reactions prior to the next dose. It is uncertain whether monitoring for hepatotoxicity will not be carried out postmarketing to the same extent as in the clinical trials, putting patients at risk for severe hepatotoxicity. Based on difficulty in the clinical trials in identifying the type of serious skin reaction that occurred in a given patient, it is uncertain whether patients or physicians will recognize at onset which skin reactions are likely to be serious.

11.2. Conditions of Use to Address Safety Issue(s)

If approved, this product should not be for first line use.

11.3. Recommendations on REMS

If this product is approved, the REMS should address the increased risk of immune mediated conditions including the liver, cutaneous reactions, colitis, sarcoidosis and other autoimmune disorders.

Dr. Rosenberg specifically recommended the following:

“Mitigation strategies that have been developed for checkpoint inhibition therapy should be employed in this setting, bearing in mind that some patients died despite implementation of such strategies. Models that evaluate these approaches as well as other approaches that may directly impact Treg numbers or functionality should be considered in informing mitigation strategies.” I agree with Dr. Rosenberg’s recommendation.

12 Postmarketing Requirements and Commitments

I recommend not approval of this product based on safety concerns. Possible postmarketing studies are being discussed internally.

Dr. Amy Rosenberg, FDA immunologist has proposed a series of studies to be conducted by the applicant to identify biomarkers or genetic/proteomic signatures that might predict autoimmunity.

1. Correlate the extent of Treg depletion coupled with CD56hiNK enhancement in patients with autoimmune mediated AEs vs those not manifesting such responses and assess whether this could be used as a basis to develop an assay to predict autoimmune AEs

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2. Develop an in vitro assay of lymphocyte proliferation (spontaneous and induced) which could potentially provide a biomarker of autoimmunity. Given the lymphoproliferation associated with loss of Treg function, this should be evaluated by the sponsor in patients who developed autoimmune AEs vs those that did not.
3. Develop an RNA-seq analysis of lymphocytes to assess for a signature of autoimmunity that could be utilized to identify informative biomarkers.
4. Assess *function* of Tregs following recovery of significant levels on cessation of DAC
5. Assess earlier biomarkers of liver injury (see enclosed paper)
6. Investigate the presence of autoantibodies to the spectrum of autoantigens observed in patients with mutations in IL-2RA and CTLA4 and their correlation to symptomatic autoimmune disease
7. Consider approaches to mitigating severe autoimmunity that consider the likely mechanism of action, Treg depletion. Given the 6 month time to recovery of such cells following cessation of DAC, strategies that would increase Treg numbers or functionality, together with other immunosuppressive agents may more rapidly reverse and prevent tissue damage.
8. The long term consequences of such treatment should be evaluated in Phase IV safety assessment.

I agree with Dr. Rosenberg's proposed studies.

13 Appendices

13.1. References

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13.2. Financial Disclosure

Please see Dr. Rodichok's review.

13.3. Additional information not presented in the body of the review

13.3.1. ELIGIBILITY CRITERIA IN STUDIES 201 and 301

- **Exclusions in study 201**
- History of - malignancy other than treated skin basal or squamous cell carcinoma
 - abnormal lab result indicative of any significant disease that would preclude administration of DAC HYP
 - HIV or other immunodeficient condition
 - drug or alcohol abuse within 2 years prior to randomization
- An MS relapse within 50 days prior to randomization or earlier, if the subject had not stabilized from that relapse
- Positive screening for Hepatitis B or C virus
- Varicella or herpes zoster or any severe viral infection within 6 weeks prior to screen
- Exposure to varicella zoster virus within 21 days before screening
- Pregnancy and breastfeeding, current or planned during the study
- Any of the following abnormal blood test at screening
 - o Hemoglobin ≤ 9.0 g/dL
 - o platelets $\leq 100 \times 10^9/L$
 - o lymphocytes $\leq 1.0 \times 10^9/L$
 - o neutrophils $\leq 1.5 \times 10^9/L$

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- o alanine aminotransferase/serum glutamate pyruvate transaminase (ALT/SGPT),
- o aspartate aminotransferase/serum glutamic oxaloacetic transaminase (AST/SGOT), or gamma-glutamyl-transferase 2x ULN
- o serum creatinine > ULN
- Treatment history
 - o Prior treatment with DAC HYP or DAC Nutley
 - o Live virus vaccine within 4 weeks before randomization
 - o Any infection requiring hospitalization or IV antibiotics within 8 weeks
 - o Elective surgery within 2 weeks prior to randomization or during the study
 - o Prior treatment with total lymphoid radiation, cladribine, mitoxantrone, Tcell or Tcell receptor vaccination, any therapeutic monoclonal antibody except for natalizumab or rituximab
 - o Prior treatment with (related to date of randomization)
 - cyclophosphamide or rituximab within one year
 - natalizumab, cyclosporine, azathioprine, methotrexate, IV Ig, plasmapheresis, within 6 months
 - any of the following: glatiramer, IFN- α or IFN- β within 3 months (subjects who were positive for neutralizing antibodies [NAbs] to IFN- β may have received IFN- β treatment up to 2 weeks)
 - intravenous (IV) or oral corticosteroids (CS), 4-aminopyridine or related products within the 30 days prior to randomization.
- Other unspecified reasons that, in the opinion of the Investigator and/or BiogenIdec, made the subject unsuitable for enrollment.

- **Exclusions in study 301**

Main Exclusion Criteria:

- Diagnosis of progressive forms of MS. These conditions required the presence of continuous clinical disease worsening over at least 3 months.
- Known intolerance, contraindication to, or history of noncompliance with IFN β 1a 30 μ g. (Note: Current or prior use of an approved IFN- β preparation for MS, including IFN β 1a, was allowed)
- History of
 - o malignancy except excised BCC.
 - o severe allergic or anaphylactic reactions (to any drug)
 - o hypersensitivity to study drug or their excipients
 - o HIV or other immunodeficient conditions
 - o Drug or alcohol abuse within 2 years of randomization
 - o Seizure disorder or unexplained blackouts or history of seizure within 6 months prior to randomization
 - o Suicidal ideation or severe depression within 3 months
 - o Positive screening test results for hepatitis C or B virus

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- History of abnormal laboratory results that, in the opinion of the Investigator, were indicative of any significant cardiac, endocrine, hematological, hepatic, immunologic, metabolic, urologic, pulmonary, gastrointestinal, dermatologic, psychiatric, renal, neurological (other than MS), and/or other major disease that would have precluded administration of DAC HYP or IFNβ1a.
- Any type of live virus vaccine from 4 weeks before randomization, including but not limited to: measles/mumps/rubella vaccine, varicella zoster virus vaccine, oral polio vaccine, and nasal influenza vaccine.
- Infection (viral, fungal, bacterial) requiring hospitalization or intravenous (IV) antibiotics within 8 weeks before randomization.
- Elective surgery performed from 2 weeks prior to randomization or scheduled through the end of the study.
- Abnormal blood tests at screening (very similar to study 201)
 - hemoglobin ≤ 9.0 g/dL
 - platelets $\leq 100 \times 10^9/L$
 - lymphocytes $\leq 1.0 \times 10^9/L$
 - neutrophils $\leq 1.5 \times 10^9/L$
 - ALT, AST or GGT $\geq 2x$ ULN (for 201 was $>2x$ ULN)
 - Serum creatinine $>ULN$
- An MS relapse that had occurred within the 50 days prior to randomization and/or the subject had not stabilized from a previous relapse prior to randomization.
- Treatment with another investigational drug or approved therapy for investigational use within the 6 months prior to randomization.
- Any previous treatment with daclizumab or other anti-CD25 monoclonal antibody.
- Prior treatment with
 - Total lymphoid irradiation, cladribine, T cell or T cell receptor vaccination, any therapeutic monoclonal antibody except natalizumab.
 - mitoxantrone, cyclophosphamide, fingolimod, or natalizumab within 1 year prior to randomization.
 - Cyclosporine, azathioprine, methotrexate, MMF, IV immunoglobulin, plasmapheresis within 6 months prior to randomization
 - Initiation of treatment or dose adjustment of fampridine-SR within 3 months prior to randomization
 - IV or oral corticosteroids, glatiramer acetate within 1 month prior to randomization (subjects receiving IFN beta are not required to washout prior to randomization but IFN beta must be discontinued prior to randomization.
 - For subjects currently taking valproic acid, carbamazepine, lamotrigine or phenytoin
 - If they were taking 1 of these medications at a stable dose for at least 6 months prior to randomization they may continue to receive the medication without alteration and are eligible for study participation.
 - The following subjects are excluded from study participation ***
 - If they initiated these agent within 6 months they should be excluded from study participation unless they discontinue the agents prior to randomization

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- Subjects treated with 2 or more of these agents for >6 months prior to randomization must be excluded unless they reduce to ≤1 agent prior to randomization
 - Subjects who have had dose escalations of one of these agents within the 6 months prior to randomization are excluded from participation unless they revert to a previous dose that was used for at least 6 months prior to randomization, or unless they discontinue the agent prior to randomization.
*** alternative medications are allowed in the protocol
 - Subjects taking isoniazid, PTU or nimesulide at the time of randomization and not able to discontinue or change to an alternative medication should be excluded.
- Miscellaneous reasons
 - Female subjects who are currently pregnant, breastfeeding or plan to become pregnant
 - Subjects from whom MRI is contraindicated
 - Unwillingness or inability to comply with protocol

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**13.3.2. Example Narrative from DAC HYP BLA application.
301/774-007 (fatal aspiration pneumonia & sepsis) as
submitted by applicant (6 pages) .**

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13.3.3. TABLES and FIGURES NOT INCLUDED IN BODY OF THE REVIEW

Table 13.3.3.1 **SERIOUS AES** in STUDY 201

	Placebo N=204		DAC 150 N= 207		DAC 300 N=208	
	n	%	n	%	n	%
ANY SAE	53	26.0	32	15.4	36	17.2
SAE excluding MS/MS relapse	12	5.9	15	7.2	18	8.6
BLOOD AND LYMPHATIC SYSTEM DISORDERS	1	0.5	0	0	1	0.5
LEUKOCYTOSIS	1	0.5	0	0	0	0
LYMPHADENOPATHY	0	0	0	0	1	0.5
CARDIAC DISORDERS	2	1.0	0	0	1	0.5
ANGINA UNSTABLE	1	0.5	0	0	0	0
ATRIAL FIBRILLATION	1	0.5	0	0	0	0
MYOCARDIAL ISCHAEMIA	0	0	0	0	1	0.5
ENDOCRINE DISORDERS	1	0.5	0	0	1	0.5
AUTOIMMUNE THYROIDITIS	0	0	0	0	1	0.5
DIABETES INSIPIDUS ¹	1	0.5	0	0	0	0
EYE DISORDERS	0	0	1	0.5	0	0
RETINAL VEIN OCCLUSION ²	0	0	1	0.5	0	0
GASTROINTESTINAL DISORDERS	1	0.5	3	1.4	2	1.0
COLITIS ISCHAEMIC	0	0	1	0.5	0	0
CROHN'S DISEASE	0	0	0	0	1	0.5
GASTRITIS	1	0.5	1	0.5	0	0
GASTRODUODENITIS	0	0	0	0	1	0.5
GASTROESOPHAGEAL REFLUX DISEASE	0	0	1	0.5	0	0
HEPATOBIILIARY DISORDERS	1	0.5	2	1.0	1	0.5
CHOLECYSTITIS CHRONIC	0	0	1	0.5	0	0
CHOLELITHIASIS	1	0.5	0	0	0	0
HEPATITIS TOXIC	0	0	1	0.5	0	0
JAUNDICE	0	0	0	0	1	0.5
IMMUNE SYSTEM DISORDERS	0	0	0	0	1	0.5
HYPERSENSITIVITY	0	0	0	0	1	0.5
INFECTIONS AND INFESTATIONS	0	0	6	2.9	3	1.4
APPENDICITIS	0	0	1	0.5	0	0
CYTOMEGALOVIRUS INFECTION	0	0	1	0.5	0	0

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GASTROENTERITIS	0	0	1	0.5	0	0
HEPATITIS B	0	0	1	0.5	0	0
PERITONSILLAR ABSCESS	0	0	0	0	1	0.5
PSOAS ABSCESS ²	0	0	1	0.5	0	0
SINUSITIS	0	0	0	0	1	0.5
URINARY TRACT INFECTION	0	0	1	0.5	0	0
VIRAL INFECTION	0	0	1	0.5	0	0
YERSINIA INFECTION	0	0	0	0	1	0.5
INJURY, POISONING AND PROCEDURAL COMPLICATIONS	2	1.0	1	0.5	0	0
BRAIN CONTUSION	1	0.5	0	0	0	0
CONTUSION	1	0.5	0	0	0	0
FEMORAL NECK FRACTURE	0	0	1	0.5	0	0
TIBIA FRACTURE	1	0.5	0	0	0	0
INVESTIGATIONS	0	0	1	0.5	0	0
ALANINE AMINOTRANSFERASE INCREASED	0	0	1	0.5	0	0
ASPARTATE AMINOTRANSFERASE INCREASED	0	0	1	0.5	0	0
METABOLISM AND NUTRITION DISORDERS	1	0.5	0	0	0	0
HYPERCHOLESTEROLAEMIA	1	0.5	0	0	0	0
HYPERGLYCAEMIA	1	0.5	0	0	0	0
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	1	0.5	0	0	0	0
BACK PAIN	1	0.5	0	0	0	0
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS)	1	0.5	1	0.5	2	1.0
CERVIX CARCINOMA	1	0.5	1	0.5	0	0
MALIGNANT MELANOMA	0	0	0	0	1	0.5
SUPERFL SPREAD MELANOMA	0	0	0	0	1	0.5
NERVOUS SYSTEM DISORDERS	45	22.1	20	9.7	22	10.6
CEREBROVASCULAR INSUFFICIENCY	0	0	1	0.5	0	0
INTRACRANIAL ANEURYSM	0	0	0	0	1	0.5
MIGRAINE	0	0	0	0	1	0.5
MULTIPLE SCLEROSIS	0	0	0	0	1	0.5
MULTIPLE SCLEROSIS RELAPSE	44	21.6	19	9.2	18	8.7

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SYNCOPE	0	0	0	0	1	0.5
TEMPORAL LOBE EPILEPSY	1	0.5	0	0	0	0
PREGNANCY, PUERPERIUM AND PERINATAL CONDITIONS>	1	0.5	0	0	0	0
ABORTION MISSED	1	0.5	0	0	0	0
PSYCHIATRIC DISORDERS>	0	0	1	0.5	0	0
MOOD DISORDER DUE TO A GENERAL MEDICAL CONDITION	0	0	1	0.5	0	0
RENAL AND URINARY DISORDERS>	0	0	0	0	1	0.5
NEPHROLITHIASIS	0	0	0	0	1	0.5
REPRODUCTIVE SYSTEM AND BREAST DISORDERS	2	1.0	1	0.5	2	1.0
CERVICAL DYSPLASIA	1	0.5	0	0	0	0
DYSFUNCTIONAL UTERINE BLEEDING	0	0	1	0.5	0	0
ENDOMETRIAL HYPERPLASIA	0	0	0	0	1	0.5
OVARIAN CYST	0	0	0	0	1	0.5
OVARIAN DISORDER	0	0	0	0	1	0.5
UTERINE POLYP	1	0.5	0	0	0	0
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	1	0.5	0	0	0	0
PLEURISY	1	0.5	0	0	0	0
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	0	0	2	1.0	3	1.4
DERMATITIS ALLERGIC	0	0	0	0	1	0.5
DERMATITIS ATOPIC	0	0	0	0	1	0.5
DERMATITIS EXFOLIATIVE	0	0	1	0.5	0	0
ERYTHEMA NODOSUM	0	0	0	0	1	0.5
RASH ²	0	0	1	0.5	0	0
VASCULAR DISORDERS	0	0	0	0	1	0.5
CIRCULATORY COLLAPSE	0	0	0	0	1	0.5

Source: Generated by FDA Medical Officer using Empirica Study from datasets submitted May 14, 2015. Events are mentioned only once within each SOC; one patient may have events in various SOCs. * SAE except MS excluded PT of multiple sclerosis and multiple sclerosis relapse (FDA MO analysis using JUMP).¹ One patient from site 903 developed a SAE of diabetes insipidus. He may have received active treatment (either DAC 150 or 300).² One patient (205MS201/304-006) had a rash leading to drug discontinuation; the patient eventually developed several serious AEs retinal thrombosis, sepsis, psoas abscess and ischemic colitis and died within the 180 day followup.

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 Tablee 13.3.3.2 **SERIOUS AES** in STUDY 301

Patients with SAE SOC PT	IFN N=922		DAC 150 N=919	
	n	%	n	%
ANY SAE (except MS relapse)*	86	9.5%	142	15.5%
ANY SAE	194	21.0%	221	24.1%
BLOOD AND LYMPHATIC SYSTEM DISORDERS	2	0.2%	12	1.4%
AGRANULOCYTOSIS	0	0	1	0.1%
ANAEMIA	1	0.1%	1	0.1%
HAEMOLYTIC ANAEMIA	0	0	1	0.1%
IRON DEFICIENCY ANAEMIA	1	0.1%	1	0.1%
LYMPHADENITIS/LYMPHADENOPATHY/LYMPHOID TISSUE HYPERPLASIA	0	0	9	0.3%
LYMPHOPENIA	0	0	1	0.1%
THROMBOCYTOPENIA	0	0	2	0.2%
CARDIAC DISORDERS	5	0.5%	3	0.4%
ACUTE MYOCARDIAL INFARCTION	3	0.3%	0	0
ANGINA UNSTABLE/CORONARY ARTERY DISEASE	1	0.1%	1	0
BRADYCARDIA	0	0	1	0.1%
CARDIO-RESPIRATORY ARREST	0	0	1	0.1%
PALPITATIONS	0	0	1	0.1%
PERICARDITIS	1	0.1%	0	0
CONGENITAL, FAMILIAL AND GENETIC DISORDERS	0	0	1	0.1%
DERMOID CYST	0	0	1	0.1%
EAR AND LABYRINTH DISORDERS	0	0	1	0.1%
VERTIGO	0	0	1	0.1%
ENDOCRINE DISORDERS	1	0.1%	1	0.1%
HYPERTHYROIDISM	1	0.1%	1	0.1%
EYE DISORDERS	0	0	1	0.1%
CYSTOID MACULAR OEDEMA	0	0	1	0.1%
GASTROINTESTINAL DISORDERS>	6	0.7%	11	1.2%
ABDOMINAL PAIN	2	0.2%	1	0.1%
ANAL FISTULA	0	0	1	0.1%
APHTHOUS STOMATITIS	0	0	1	0.1%
COLITIS MICROSCOPIC	0	0	1	0.1%
COLITIS ULCERATIVE	0	0	1	0.1%
CONSTIPATION	1	0.1%	0	0
DIARRHOEA	0	0	1	0.1%
ENTEROCOLITIS	0	0	1	0.1%
GASTRITIS EROSIVE	0	0	1	0.1%

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HAEMORRHOIDS	0	0	1	0.1%
INGUINAL HERNIA	1	0.1%	2	0.2%
MOUTH CYST	1	0.1%	0	0
NAUSEA	0	0	1	0.1%
OROANTRAL FISTULA	1	0.1%	0	0
VOMITING	0	0	1	0.1%
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	1	0.1%	3	0.4%
ASTHENIA	0	0	1	0.1%
CHEST PAIN	0	0	1	0.1%
INFLUENZA LIKE ILLNESS	1	0.1%	0	0
MULTI-ORGAN FAILURE	0	0	1	0.1%
HEPATOBIILIARY DISORDERS	4	0.4%	7	0.8%
ACUTE HEPATIC FAILURE	0	0	1	0.1%
CHOLECYSTITIS	0	0	1	0.1%
CHOLELITHIASIS	3	0.3%	1	0.1%
DRUG-INDUCED LIVER INJURY	0	0	1	0.1%
HEPATITIS ACUTE	0	0	1	0.1%
HEPATITIS TOXIC	1	0.1%	2	0.2%
IMMUNE SYSTEM DISORDERS	1	0.1%	1	0.1%
ANAPHYLACTIC REACTION	1	0.1%	0	0
DRUG HYPERSENSITIVITY	0	0	1	0.1%
INFECTIONS AND INFESTATIONS	15	1.6%	40	4.6%
APPENDICITIS/APPENDICITIS PERFORATED	0	0	3	0.3%
BACTERIAL INFECTION	0	0	1	0.1%
BRONCHITIS	1	0.1%	0	0
CELLULITIS	0	0	2	0.2%
CHRONIC TONSILLITIS	0	0	1	0.1%
CYSTITIS/URINARY TRACT INFECTION	0	0	1	0.1%
DENGUE FEVER	0	0	1	0.1%
DEVICE RELATED INFECTION	0	0	1	0.1%
EAR INFECTION	0	0	1	0.1%
ENTERITIS/ENTEROCOLITIS INFECTIOUS	0	0	2	0.2%
ERYSIPELAS	1	0.1%	0	0
FUNGAL INFECTION	0	0	1	0.1%
HEPATITIS A	0	0	1	0.1%
INFLUENZA	0	0	1	0.1%
INTERVERTEBRAL DISCITIS	1	0.1%	0	0
LUDWIG ANGINA	0	0	1	0.1%
LUNG INFECTION	0	0	1	0.1%
LYME DISEASE	1	0.1%	1	0.1%

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MENINGITIS VIRAL	0	0	1	0.1%
NEUROBORRELIOSIS	0	0	1	0.1%
PAROTITIS	0	0	1	0.1%
PELVIC ABSCESS	0	0	1	0.1%
PERIRECTAL ABSCESS	1	0.1%	0	0
PERITONITIS	1	0.1%	0	0
PNEUMONIA/LOBAR PNEUMONIA	2	0.2%	6	0.8%
PULMONARY TUBERCULOSIS	0	0	1	0.1%
PYELONEPHRITIS/PYELONEPHRITIS ACUTE	1	0.1%	2	0.2%
REITER'S SYNDROME	0	0	1	0.1%
SEPSIS/UROSEPSIS	1	0.1%	1	0.2%
STRONGYLOIDIASIS	1	0.1%	0	0
UPPER RESPIRATORY TRACT INFECTION	0	0	1	0.1%
URINARY TRACT INFECTION	2	0.2%	8	0.9%
VARICELLA	1	0.1%	1	0.1%
VIRAL INFECTION	1	0.1%	2	0.2%
VIRAL MYOCARDITIS	1	0.1%	0	0
INJURY, POISONING AND PROCEDURAL COMPLICATIONS	8	0.9%	9	1.2%
ANKLE FRACTURE	2	0.2%	2	0.2%
CLAVICLE FRACTURE	0	0	1	0.1%
CONCUSSION	1	0.1%	0	0
FACE INJURY	1	0.1%	0	0
FALL	2	0.2%	4	0.5%
FIBULA FRACTURE	1	0.1%	2	0.2%
FOREIGN BODY	0	0	1	0.1%
HAND FRACTURE	1	0.1%	0	0
HIP FRACTURE	0	0	1	0.1%
LIGAMENT INJURY OR RUPTURE	2	0.2%	0	0
MENISCUS INJURY	1	0.1%	0	0
MULTIPLE INJURIES	1	0.1%	0	0
NAIL AVULSION	0	0	1	0.1%
POST PROCEDURAL HAEMORRHAGE	0	0	1	0.1%
ROAD TRAFFIC ACCIDENT	2	0.2%	0	0
TIBIA FRACTURE	0	0	1	0.1%
INVESTIGATIONS	3	0.3%	3	0.3%
ALANINE AMINOTRANSFERASE INCREASED	2	0.2%	0	0
AMYLASE INCREASED	0	0	1	0.1%
ASPARTATE AMINOTRANSFERASE INCREASED	2	0.2%	0	0
HEPATIC ENZYME INCREASED	0	0	1	0.1%
SMEAR CERVIX ABNORMAL	0	0	1	0.1%

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TRANSAMINASES INCREASED	1	0.1%	0	0
METABOLISM AND NUTRITION DISORDERS	0	0	4	0.4%
DEHYDRATION	0	0	1	0.1%
DIABETICKETOACIDOSIS	0	0	1	0.1%
HYPOKALAEMIA	0	0	1	0.1%
TETANY	0	0	1	0.1%
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	3	0.3%	6	0.7%
BACK PAIN	1	0.1%	0	0
BURSITIS	0	0	1	0.1%
FIBROMYALGIA	1	0.1%	0	0
INTERVERTEBRALDISC PROTRUSION	0	0	1	0.1%
LUPUS-LIKE SYNDROME	0	0	1	0.1%
PATELLOFEMORAL PAIN SYNDROME	1	0.1%	0	0
PLICA SYNDROME	0	0	1	0.1%
SPINAL OSTEOARTHRITIS	0	0	1	0.1%
SPONDYLOARTHROPATHY	0	0	1	0.1%
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS)	11	1.2%	14	1.5%
ADENOMA BENIGN	0	0	1	0.1%
BENIGN NEOPLASM	0	0	1	0.1%
BENIGN OVARIAN TUMOUR	0	0	1	0.1%
BENIGN SALIVARY GLAND NEOPLASM	0	0	2	0.2%
BRAIN NEOPLASM MALIGNANT	0	0	1	0.1%
ENDOMETRIAL CANCER	1	0.1%	0	0
FIBROADENOMA OF BREAST	1	0.1%	0	0
INVASIVE DUCTAL BREAST CARCINOMA	0	0	1	0.1%
MALIGNANT MELANOMA	1	0.1%	0	0
MENINGIOMA	0	0	1	0.1%
OVARIAN GERM CELL TERATOMA BENIGN	1	0.1%	0	0
PANCREATIC CARCINOMA METASTATIC	1	0.1%	0	0
SQUAMOUS CELL CA	1	0.1%	0	0
SQUAMOUS CELL CA OF THE CERVIX	1	0.1%	0	0
SQUAMOUS CELL CA OF THE ORAL CAVITY	1	0.1%	0	0
TESTICULAR SEMINOMA (PURE)	1	0.1%	0	0
THYROID CANCER	0	0	1	0.1%
TONGUE NEOPLASM MALIGNANT STAGE UNSPECIFIED	1	0.1%	0	0
TRANSITIONAL CELL CARCINOMA	0	0	1	0.1%
UTERINE CANCER	0	0	1	0.1%
UTERINE LEIOMYOMA	1	0.1%	3	0.3%
NERVOUS SYSTEM DISORDERS (ANY)	131	14.2%	109	11.9%

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NERVOUS SYSTEM DISORDERS (Excluding MS)*	8	0.9%	14	1.5%
COMPLEX PARTIAL SEIZURES	0	0	1	0.1%
CONVULSION/EPILEPSY	2	0.2%	4	0.4%
DIZZINESS	0	0	1	0.1%
HEADACHE	0	0	1	0.1%
MIGRAINE	0	0	1	0.1%
MULTIPLE SCLEROSIS	3	0.3%	2	0.2%
MULTIPLE SCLEROSIS RELAPSE	124	13.4%	97	10.6%
MUSCLE SPASTICITY	1	0.1%	0	0
MYASTHENIA GRAVIS	0	0	1	0.1%
OPTIC NEURITIS	1	0.1%	0	0
RELAPSING-REMITTING MULTIPLE SCLEROSIS	1	0.1%	0	0
SCIATICA	0	0	1	0.1%
SPEECH DISORDER	1	0.1%	0	0
STATUS EPILEPTICUS	0	0	1	0.1%
TENSION HEADACHE	1	0.1%	0	0
TOXIC ENCEPHALOPATHY	0	0	1	0.1%
TRANSIENT ISCHAEMIC ATTACK	0	0	1	0.1%
TRIGEMINAL NEURALGIA	1	0.1%	0	0
UHTHOFF'S PHENOMENON	0	0	1	0.1%
PREGNANCY, PUERPERIUM AND PERINATAL CONDITIONS	4	0.4%	3	0.5%
ABORTION SPONTANEOUS	1	0.1%	3 ¹	0.3%
ECTOPIC PREGNANCY	3	0.3%	2	0.2%
PSYCHIATRIC DISORDERS	8	0.9%	6	0.7%
ADJUSTMENT DISORDER WITH MIXED DISTURBANCE OF EMOTION AND CONDUCT	1	0.1%	0	0
ANXIETY	0	0	1	0.1%
BIPOLAR DISORDER	1	0.1%	0	0
COMPLETED SUICIDE	1	0.1%	0	0
DEPRESSION	2	0.2%	3	0.3%
DEPRESSION SUICIDAL	0	0	1	0.1%
EMOTIONAL DISTRESS	1	0.1%	0	0
MOOD DISORDER DUE TO A GENERAL MEDICAL CONDITION	0	0	1	0.1%
SUBSTANCE ABUSE	0	0	1	0.1%
SUICIDAL IDEATION	1 ¹	0.1%	1	0.1%
SUICIDE ATTEMPT	2	0.2%	0	0
RENAL AND URINARY DISORDERS	2	0.2%	4	0.4%
CALCULUS URETERIC/CALCULUS URINARY/NEPHROLITHIASIS	1	0	3	0.3%
HYDRONEPHROSIS	0	0	1	0.1%

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RENAL COLIC	0	0	1	0.1%
URINARY RETENTION	1	0.1%	0	0
REPRODUCTIVE SYSTEM AND BREAST DISORDERS	3	0.3%	3	0.3%
ADENOMYOSIS	0	0	1	0.1%
ENDOMETRIAL DISORDER/ENDOMETRIOSIS	0	0	2	0.2%
METRORRHAGIA	1	0.1%	0	0
OVARIAN CYST	1	0.1%	2	0.3%
UTERINE POLYP	1	0.1%	0	0
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	1	0.1%	6	0.7%
ASTHMA	0	0	1	0.1%
DYSPHONIA	0	0	1	0.1%
INTERSTITIAL LUNG DISEASE	0	0	1	0.1%
PLEURISY	1	0.1%	0	0
PNEUMONIA ASPIRATION	0	0	1	0.1%
PULMONARY EMBOLISM	0	0	2	0.2%
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	1	0.1%	14	1.5%
ANGIOEDEMA	0	0	2	0.2%
DECUBITUS ULCER	0	0	1	0.1%
DERMAL CYST	1	0.1%	0	0
DERMATITIS	0	0	3	0.3%
DRUG REACTION WITH EOSINOPHILIA AND SYSTEMIC SYMPTOMS	0	0	1	0.1%
LEUKOCYTOCLASTIC VASCULITIS	0	0	1	0.1%
LICHENOID KERATOSIS	0	0	1	0.1%
PITYRIASIS RUBRA PILARIS	0	0	1	0.1%
PSORIASIS/PUSTULAR PSORIASIS	0	0	2	0.2%
RASH MACULO-PAPULAR	0	0	1	0.1%
TOXIC SKIN ERUPTION	0	0	1	0.1%
SURGICAL AND MEDICAL PROCEDURES	2	0.2%	5	0.5%
ABORTION INDUCED	0	0	1	0.1%
ANGIOPLASTY	0	0	1	0.1%
HYSTERECTOMY	1	0.1%	1	0.1%
OVARIAN CYSTECTOMY	1	0.1%	0	0
REHABILITATION THERAPY	0	0	1	0.1%
SPINAL DECOMPRESSION	0	0	1	0.1%
VASCULAR DISORDERS	2	0.2%	4	0.4%
DEEP VEIN THROMBOSIS	0	0	1	0.1%
HYPOTENSION	0	0	1	0.1%
KAWASAKI'S DISEASE	0	0	1	0.1%
VARICOSE VEIN	1	0.1%	0	0

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VASCULITIS	0	0	1	0.1%
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Source: FDA Medical Officer analysis, Empirica Study, May 14, 2015 datasets. Number of patients with AE excluding MS calculated from ADAM AE dataset using JUMP. Table includes events up to 180 days after last dose. SOC: System Organ Class. MedDRA 16.0. One patient may have more than one event but is counted once within each SOC.

To go back to Section 8.4.2 SAEs, click here 8.4.2.

To go to Section 8.4.3 click here 8.4.3

Table 13.3.3.3 DAC HYP BLA, study 201, AE leading to **DRUG DISCONTINUATION**

System Organ Class Adverse Event	Placebo N= 204		DAC HYP 150 N= 207		DAC HYP 300 N=208	
	n	%	n	%	n	%
AE leading to treatment discontinuation	2	1.0	6	2.9	9	4.3
CONGENITAL FAMILIAL & GENETIC DISORDERS	1	0.5	0	0	0	0
Gilbert's syndrome	1	0.5	0	0	0	0
HEPATOBIILIARY DISORDERS	0	0	0	0	1	0.5
Jaundice	0	0	0	0	1	0.5
IMMUNE SYSTEM DISORDERS	0	0	0	0	1	0.5
Hypersensitivity	0	0	0	0	1	0.5
INFECTIONS & INFESTATIONS	0	0	1	0.5	1	0.5
Hepatitis B	0	0	1	0.5	0	0
Yersinia infection	0	0	0	0	1	0.5
INVESTIGATIONS	1	0.5	3	1.4	1	0.5
ALT increased	0	0	1	0.5	0	0
AST increased	0	0	1	0.5	0	0
Hepatic enzyme increased	0	0	2	1.0	0	0
Blood BR increased	1	0.5	0	0	0	0
Blood LDH increased	0	0	0	0	1	0.5
NEOPLASMS, BENIGN, MALIGNANT and UNSPEC.	1	0.5	0	0	0	0
Cervix carcinoma	1	0.5	0	0	0	0
NERVOUS SYSTEM DISORDERS	0	0	0	0	3	1.4
MS relapse	0	0	0	0	1	0.5
Presyncope	0	0	0	0	1	0.5
Syncope	0	0	0	0	1	0.5
REPRODUCTIVE SYSTEM AND BREAST DISORDERS	0	0	0	0	1	0.5
Endometrial hyperplasia	0	0	0	0	1	0.5
Ovarian disorder	0	0	0	0	1	0.5
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	0	0	3	1.4	3	1.4
Alopecia	0	0	1	0.5	0	0
Dermatitis exfoliative	0	0	1	0.5	0	0
Rash maculo-papular	0	0	1	0.5	0	0
Toxic skin eruption	0	0	1	0.5	0	0

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Dermatitis allergic	0	0	0	0	1	0.5
Erythema nodosum	0	0	0	0	1	0.5
Rash	0	0	0	0	1	0.5
VASCULAR DISORDERS	0	0	0	0	1	0.5
Circulatory collapse	0	0	0	0	1	0.5

Source: ADAE submitted May 14, 2015.

Table 13.3.3.4. DAC HYP BLA, study 301. AE leading to **DRUG DISCONTINUATION**

Body System Adverse Event	30 ug IFNβ1a N=922		DAC 150 N=919	
	n	%	n	%
ANY BODY SYSTEM /ANY EVENT	110	11.9	141	15.3
ANY AE excluding MS/MS Relapse*	107	11.6	139	15.1
BLOOD AND LYMPHAT	3	0.3	8	0.9
AGRANULOCYTOSIS	0	-	1	0.1
IRON DEFICIENCY ANAEMIA	1	0.1	0	-
LYMPHADENOPATHY	0	-	5	0.5
LYMPHOPENIA	2	0.2	2	0.2
CARDIAC DISORDERS	1	0.1	1	0.1
Bradycardia	0	-	1	0.1
Pericarditis	1	0.1	0	-
ENDOCRINE DISORDE	0	-	1	0.1
Autoimmune Thyroiditis	0	-	1	0.1
GASTROINTESTINAL	1	0.1	3	0.3
Colitis	0	-	1	0.1
Colitis Ulcerative	0	-	1	0.1
Flatulence	1	0.1	0	-
Plicated Tongue	0	-	1	0.1
GENERAL DISORDERS	11	1.2	6	0.7%
Asthenia	1	0.1	0	-
Face Edema	1	0.1	0	-
Gait Disturbance	0	-	1	0.1%
Influenza Like Illness	7	0.8	0	-
Injection Site Erythema	0	-	2	0.2%
Injection Site Pain	0	-	1	0.1%
Injection Site Reaction	1	0.1	0	0%
Local Swelling	0	-	1	0.1%
Multi-Organ Failure	0	-	1	0.1%
Pyrexia	1	0.1	0	-

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HEPATOBIILIARY DIS	3	0.3	7	0.8
Acute Hepatic Failure	0	-	1	0.1
Biliary Colic	0	-	1	0.1
Drug-Induced Liver Injury	0	-	1	0.10
Hepatitis Acute	0	-	1	0.10
Hepatitis Toxic	1	0.1	2	0.20
Hepatotoxicity	0	-	1	0.10
Hyperbilirubinaemia	1	0.1	0	-
Hypertransaminasaemia	1	0.1	0	-
IMMUNE SYSTEM DISORDER	1	0.1	1	0.1
Anaphylactic Reaction	1	0.1	0	-
Sarcoidosis	0	-	1	0.1
INFECTIONS AND INFESTATIONS DISORDERS	3	0.3	5	0.5
Folliculitis	1	0.1	0	-
HIV Infection	1	0.1	0	-
Peritonitis	1	0.1	0	-
Pharyngitis	0	-	1	0.1
Pneumonia	0	-	1	0.1
Pulmonary Tuberculosis	0	-	1	0.1
Tuberculosis	0	-	1	0.1
Urinary Tract Infection	0	-	1	0.1
INVESTIGATIONS	35	3.8	45	4.9
ALT Increased	13	1.4	18	2.0
Amylase Increased	1	0.1	0	-
AST Increased	9	1.0	7	0.8
Blood Alkaline Phosphatase Increased	0	-	1	0.1
Blood Bilirubin Increased	1	0.1	2	0.2
Fibrin D Dimer Increased	1	0.1	0	-
GGT Creased	1	0.1	2	0.2
Hepatic Enzyme Increased	4	0.4	4	0.4
Liver Function Test Abnormal	11	1.2	16	1.7
Lymphocyte Count Decreased	0	-	3	0.3
Transaminases Increased	3	0.3	0	-
MUSCULOSKELETAL AND CONNECTIVE TISSUE	0	-	3	0.3
Arthritis	0	-	1	0.1
Lupus-Like Syndrome	0	-	1	0.1
Seronegative Arthritis	0	-	1	0.1
NEOPLASMS BENIGN, MALIGNANT, etc.	8	0.9	4	0.4
Brain Neoplasm Malignant	0	-	1	0.1
Endometrial Cancer	1	0.1	0	-
Invasive Ductal Breast Carcinoma	0	-	1	0.1
Malignant Melanoma	1	0.1	0	-

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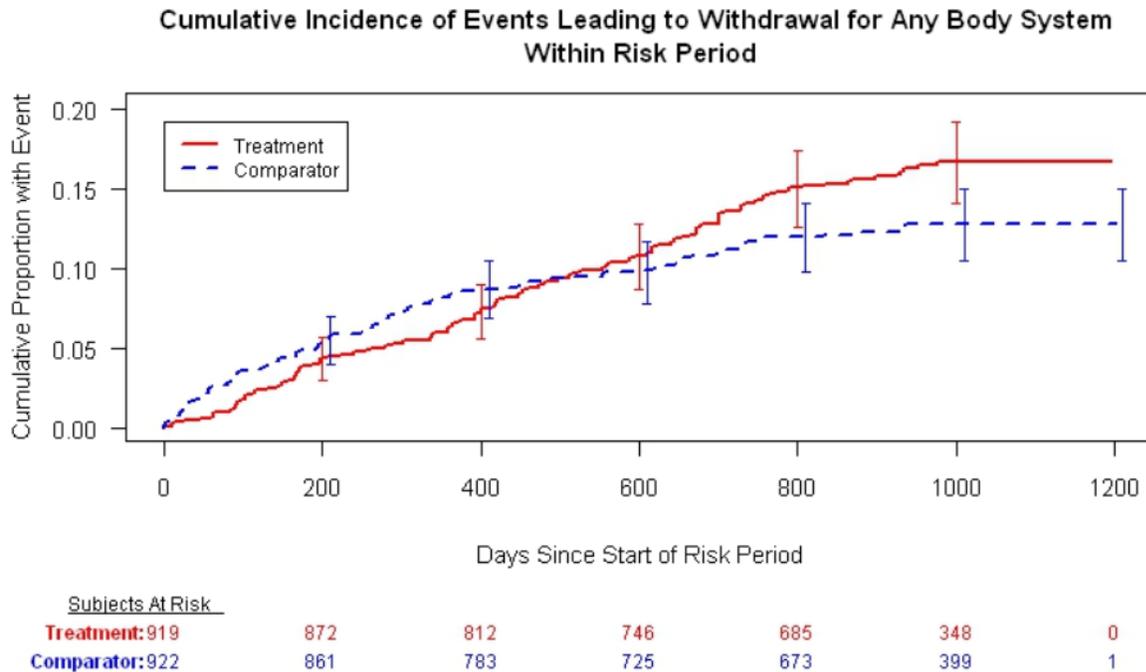
Pancreatic Carcinoma Metastatic	1	0.1	0	-
Squamous Cell Carcinoma	1	0.1	0	-
Squamous Cell Carcinoma Of The Cervix	1	0.1	0	-
Squamous Cell Carcinoma Of The Oral Cavity	1	0.1	0	-
Testicular Seminoma (Pure)	1	0.1	0	-
Tongue Neoplasm Malig Stage Unspecified	1	0.1	0	-
Uterine Cancer	0	-	1	0.1
Uterine Leiomyoma	0	-	1	0.1
NERVOUS SYSTEM DISORDERS	32	3.5	14	1.5
Central Nervous System Lesion	1	0.1	0	-
Convulsion	1	0.1	0	-
Headache	0	-	1	0.1
Multiple Sclerosis/MS relapse	29	3.0	12	1.3
Paraesthesia	1	0.1	0	-
Status Epilepticus	0	-	1	0.1
PSYCHIATRIC DISOR	6	0.7	1	0.1
Completed Suicide	1	0.1	0	-
Depression	2	0.2	0	-
Social Avoidant Behavior	1	0.1	0	-
Suicidal Ideation	1	0.1	1	0.1
Suicide Attempt	1	0.1	0	0%
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	1	0.1	6	0.7
ASTHMA	0	0	1	0.1
DYSPHONIA	0	0	1	0.1
INTERSTITIAL LUNG DISEASE	0	0	1	0.1
PLEURISY	1	0.1	0	0
PNEUMONIA ASPIRATION	0	0	1	0.1
PULMONARY EMBOLISM	0	0	2	0.2
SURGICAL AND MEDICAL PROCEDURES	2	0.2	5	0.5
ABORTION INDUCED	0	0	1	0.1
ANGIOPLASTY	0	0	1	0.1
HYSTERECTOMY	1	0.1	1	0.1
OVARIAN CYSTECTOMY	1	0.1	0	0
REHABILITATION THERAPY	0	0	1	0.1
SPINAL DECOMPRESSION	0	0	1	0.1

VASCULAR DISORDERS	2	0.2	4	0.4
DEEP VEIN THROMBOSIS	0	0	1	0.1
HYPOTENSION	0	0	1	0.1
KAWASAKI'S DISEASE	0	0	1	0.1
VARICOSE VEIN	1	0.1	0	0
VASCULITIS	0	0	1	0.1

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Source: FDA Medical Officer analysis, Empirica Study, May 14, 2015 datasets. Number of patients with AE excluding MS calculated from ADAM AE dataset using JUMP. Table includes events up to 180 days after last dose. SOC: System Organ Class. MedDRA 16.1. One patient may have more than one event but is counted once within each SOC. Five patients had neurologic events not coded as MS relapse that led to drug withdrawal (3 on IFN, 2 on DAC HYP), although they may have been manifestations of MS relapse.

FIGURE. Time to event plot. AE leading to drug discontinuation in study 301.



Source: Empirica Study. Run by Dr. Villalba

To go back to Section 8.4.3, AE leading to drug discontinuation click here [8.4.3](#)

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13.3.3.5 Most common AE by PT in study 201		150 mg DAC HYP		300 mg DAC HYP		Placebo	
Body System or Organ Class	Dictionary-Derived Term	N=208		N=209		N=204	
		Subject Count	%	Subject Count	%	Subject Count	%
Nervous System Disorders	Multiple Sclerosis Relapse	47	22.6	42	20.1	77	37.7
Infections And Infestations	Nasopharyngitis	30	14.4	30	14.4	31	15.2
Nervous System Disorders	Headache	20	9.6	20	9.6	21	10.3
Infections And Infestations	Upper Respiratory Tract Infection	18	8.7	22	10.5	14	6.9
Infections And Infestations	Pharyngitis	13	6.3	13	6.2	9	4.4
Skin And Subcutaneous Tissue Disorders	Rash	12	5.8	11	5.3	6	2.9
Infections And Infestations	Oral Herpes	10	4.8	13	6.2	10	4.9
Investigations	Alanine Aminotransferase Increased	10	4.8	12	5.7	4	2.0
Psychiatric Disorders	Depression	10	4.8	12	5.7	3	1.5
Infections And Infestations	Urinary Tract Infection	9	4.3	10	4.8	9	4.4
Infections And Infestations	Rhinitis	9	4.3	6	2.9	3	1.5
Infections And Infestations	Respiratory Tract Infection Viral	8	3.8	10	4.8	5	2.5
Musculoskeletal And Connective Tissue Disorders	Back Pain	8	3.8	10	4.8	10	4.9
Gastrointestinal Disorders	Diarrhoea	7	3.4	8	3.8	4	2.0
General Disorders And Administration Site Conditions	Pyrexia	7	3.4	15	7.2	2	1.0
Infections And Infestations	Respiratory Tract Infection	7	3.4	13	6.2	11	5.4
Investigations	Aspartate Aminotransferase Increased	7	3.4	6	2.9	2	1.0
Blood And Lymphatic System Disorders	Anaemia	6	2.9	4	1.9	1	0.5
General Disorders And Administration Site Conditions	Fatigue	6	2.9	9	4.3	10	4.9
General Disorders And Administration Site Conditions	Influenza Like Illness	6	2.9	5	2.4	6	2.9
Respiratory, Thoracic And Mediastinal Disorders	Oropharyngeal Pain	6	2.9	5	2.4	4	2.0
Gastrointestinal Disorders	Vomiting	5	2.4	5	2.4	1	0.5
Gastrointestinal Disorders	Constipation	5	2.4	2	1.0	2	1.0
General Disorders And Administration Site Conditions	Injection Site Haematoma	5	2.4	5	2.4	2	1.0
Infections And Infestations	Influenza	5	2.4	12	5.7	11	5.4
Infections And Infestations	Cystitis	5	2.4	2	1.0	3	1.5
Injury, Poisoning And Procedural Complications	Fall	5	2.4	1	0.5	2	1.0
Musculoskeletal And Connective Tissue Disorders	Pain In Extremity	5	2.4	5	2.4	5	2.5
Musculoskeletal And Connective Tissue Disorders	Musculoskeletal Pain	5	2.4	1	0.5	1	0.5
Psychiatric Disorders	Insomnia	5	2.4	2	1.0	4	2.0
Psychiatric Disorders	Depressed Mood	5	2.4	2	1.0	1	0.5
Skin And Subcutaneous Tissue Disorders	Pruritus	5	2.4	2	1.0	5	2.5

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13.3.3.6 Most common AE by PT in study 301		150 mg DAC HYP and Avonex placebo		30 ug Avonex and DAC HYP placebo	
Body System or Organ Class	Dictionary-Derived Term	N=919		N=922	
		Subject Count	%	Subject Count	%
Nervous System Disorders	Multiple Sclerosis Relapse	299	32.5	432	46.9
Infections And Infestations	Nasopharyngitis	226	24.6	197	21.4
Nervous System Disorders	Headache	159	17.3	175	19.0
Infections And Infestations	Upper Respiratory Tract Infection	149	16.2	124	13.4
General Disorders And Administration Site Cond	Pyrexia	104	11.3	133	14.4
General Disorders And Administration Site Cond	Injection Site Pain	96	10.4	102	11.1
Infections And Infestations	Urinary Tract Infection	96	10.4	99	10.7
General Disorders And Administration Site Cond	Influenza Like Illness	88	9.6	345	37.4
Musculoskeletal And Connective Tissue Disorde	Back Pain	86	9.4	71	7.7
Infections And Infestations	Influenza	83	9.0	56	6.1
Infections And Infestations	Pharyngitis	77	8.4	69	7.5
Psychiatric Disorders	Depression	75	8.2	57	6.2
Musculoskeletal And Connective Tissue Disorde	Arthralgia	71	7.7	62	6.7
General Disorders And Administration Site Cond	Fatigue	69	7.5	75	8.1
Investigations	Alanine Aminotransferase Increased	69	7.5	67	7.3
Respiratory, Thoracic And Mediastinal Disorders	Oropharyngeal Pain	69	7.5	41	4.4
Gastrointestinal Disorders	Diarrhoea	67	7.3	55	6.0
Skin And Subcutaneous Tissue Disorders	Rash	64	7.0	26	2.8
Infections And Infestations	Bronchitis	61	6.6	43	4.7
Infections And Infestations	Oral Herpes	57	6.2	44	4.8
Musculoskeletal And Connective Tissue Disorde	Pain In Extremity	55	6.0	58	6.3
Nervous System Disorders	Hypoaesthesia	54	5.9	54	5.9
Respiratory, Thoracic And Mediastinal Disorders	Cough	53	5.8	46	5.0
Nervous System Disorders	Dizziness	49	5.3	37	4.0
Gastrointestinal Disorders	Nausea	48	5.2	46	5.0
Investigations	Aspartate Aminotransferase Increased	48	5.2	46	5.0
Blood And Lymphatic System Disorders	Lymphadenopathy	47	5.1	7	0.8
Musculoskeletal And Connective Tissue Disorde	Myalgia	42	4.6	49	5.3
Infections And Infestations	Sinusitis	41	4.5	40	4.3
Psychiatric Disorders	Insomnia	41	4.5	54	5.9
General Disorders And Administration Site Cond	Injection Site Erythema	40	4.4	47	5.1
Nervous System Disorders	Paraesthesia	40	4.4	57	6.2
Skin And Subcutaneous Tissue Disorders	Eczema	40	4.4	13	1.4
Investigations	Liver Function Test Abnormal	39	4.2	29	3.1
General Disorders And Administration Site Cond	Asthenia	38	4.1	55	6.0
Infections And Infestations	Tonsillitis	38	4.1	17	1.8
Psychiatric Disorders	Anxiety	38	4.1	34	3.7
Blood And Lymphatic System Disorders	Anaemia	36	3.9	28	3.0
Infections And Infestations	Rhinitis	33	3.6	33	3.6
Ear And Labyrinth Disorders	Vertigo	32	3.5	23	2.5
Gastrointestinal Disorders	Vomiting	32	3.5	25	2.7
Gastrointestinal Disorders	Constipation	30	3.3	25	2.7
Gastrointestinal Disorders	Toothache	30	3.3	23	2.5
Injury, Poisoning And Procedural Complications	Fall	29	3.2	32	3.5
Musculoskeletal And Connective Tissue Disorde	Muscular Weakness	29	3.2	36	3.9
Skin And Subcutaneous Tissue Disorders	Acne	29	3.2	9	1.0

AE with incidence >2% and at least 1% greater than comparator. Source: JumpStart Standard analysis catalog. Analysis run date: 2015-03-26 1:06:41 AM
 To go back to Section 8.4.4, Treatment emergent AEs click here 8.4.4.

APPEARS THIS WAY ON ORIGINAL

Reference ID: 3906449

Psychiatric Disorders	Abdominal Pain	27	2.9	27	2.9
Musculoskeletal And Connective Tissue Disorde	Neck Pain	27	2.9	20	2.2
Skin And Subcutaneous Tissue Disorders	Seborrhoeic Dermatitis	27	2.9	4	0.4
Gastrointestinal Disorders	Dyspnoea	26	2.8	17	1.8

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Table 13.3.3.7 AE in patients at site 903 of study 201

ID	Assigned Treatment	AE
205MS201/903-002	DAC HYP 150	DERMATITIS ALLERGIC, NASOPHARYNGITIS
205MS201/903-004	Placebo	ARTHRITIS, MULTIPLE SCLEROSIS RELAPSE
205MS201/903-005	DAC HYP 150	DERMATITIS ALLERGIC, STOMATITIS
205MS201/903-006	DAC HYP 300	None
205MS201/903-007	DAC HYP 300	None
205MS201/903-008	Placebo	MULTIPLE SCLEROSIS RELAPSE
205MS201/903-009	DAC HYP 150	FOOD POISONING, RASH
205MS201/903-010	Placebo	RASH
205MS201/903-011	DAC HYP 300	NASOPHARYNGITIS
205MS201/903-012	Placebo	DIABETES INSIPIDUS (Serious), RENAL CYST
205MS201/903-013	Placebo	NASOPHARYNGITIS
205MS201/903-015	Placebo	ABDOMINAL PAIN UPPER, INSOMNIA, RENAL COLIC, SYNCOPE
205MS201/903-018	DAC HYP 300	NASOPHARYNGITIS
205MS201/903-019	DAC HYP 150	None
205MS201/903-020	Placebo	NASOPHARYNGITIS
205MS201/903-021	DAC HYP 300	DERMATITIS ALLERGIC, BRONCHITIS, GASTRITIS, HYPERTENSION, INFLUENZA, NASOPHARYNGITIS
205MS201/903-022	DAC HYP 150	PHARYNGITIS, UTERINE LEIOMYOMA
205MS201/903-023	DAC HYP 300	RASH
205MS201/903-024	Placebo	NASOPHARYNGITIS, TONSILLITIS
205MS201/903-025	DAC HYP 150	LOBAR PNEUMONIA, TONSILLITIS
205MS201/903-026	DAC HYP 150	NASOPHARYNGITIS

There were 21 subjects, of whom 18 had AEs (8, 6 and 4 in the Placebo, DAC 150 and DAC 300 treatment groups, respectively). The pattern of AEs is not inconsistent with what one would expect for placebo (e.g. 2 subjects had MS relapse on placebo) or DAC (3 subjects had allergic dermatitis) and it is likely that not all patients received the wrong treatment. I agree with including these patients in the safety analyses.

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13.3.4. HEPATOBILIARY SOC AND INVESTIGATIONS, HEPATOBILIARY HLG, SAE and DROPOUTS

13.3.4.1 Listings of SERIOUS DILI (for section 8.4.2, SAE)

	ID	PT	Dx as per narrative	STDAY	Total Doses of DAC received	Confounding
1	201 454 019	Jaundice		336	58	
2	201 763-004	Hepatitis toxic	Toxic allergic hepatitis.	428	13	No HepE testing
3	201 763-011	ALT & AST Incr	ALT 17xULN	309	11	
4	301 453-026	DILI	Drug induced hepatitis.	59	3	
5	301 604-040	Hepatitis acute	Acute hepatitis.	394	14	Carbamaz, gabapentin, analgesics
6	301 110-006	Toxic hepatitis	Chemical hepatitis	207	7	Carbamaz, gabapentin, APAP
7	301 624-012	Acute hepatic failure	Drug induced hepatic failure (AIH in Diff dx) associated with serious drug eruption. <i>Had Bx.</i>	197	8	Carbamazepine & valproate
8	301 670-035	Toxic hepatitis	Autoimmune hepatitis as per consultant hepatologist. + ASMA 1:20. <i>Had Bx. Rx CS. Not Resolved.</i>	496	17	
9	202 909-001	AIH	Autoimmune hepatitis (FATAL hepatic failure). Autopsy.	668	17	
10	302 622-103	AIH	Autoimmune hepatitis. Hx of Hashimoto's thyroiditis. <i>Had Bx. Rx CS+AZA Event occurred in June 2012. As of July 2015 still on aza.</i>	119	5	Lamotrigine
11	202 765-003	Chronic hepatitis	Chronic autoimmune hepatitis.	771	25	PTU and carbamazole for AI thyroiditis
12	203 508 012	Hepatitis	AIH. Had Bx. Hepatocellular and cholestatic		29	

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			component. Treated with CS.			
13	203 506-011	AIH	Autoimmune hepatitis. Rx CS	1382	49	IV MP 2 months earlier
14	203 508 -016	Hepatitis	Elevated ALT (x9ULN, normal BR). Skin rash hands	1467	52	Amoxicillin
15	203/512-103*	Liver enzymes	ALT >3x ULN. BR >2xULN after cutoff of SUR	UNK	31	Amoxicillin
16	203 759-008	Hepatocellular Jaundice r	US: steatosis, hepatomegaly, chronic cholecystitis, also had toxic drug eruption	1440	50	
17	303 649 009	Jaundice, DILI	Autoimmune hepatitis/ thrombocytopenia. Rx: CS	161	4	
18	303 680-001	Hepatitis toxic	Toxic hepatitis/ acute hepatic cytolysis 2nd to Rx, also had HTN cardiomyopathy	1065	38	

Additionally patient 301/670-024 had “Hepatic enzyme increased”. The HAC and Dr. Avigan believe this is infectious cholangitis not related to DAC HYP. In my opinion this could be mixed hepatocellular and cholestatic DAC HYP induced DILI with cholangitis component. As per an infectologist consultant this case was autoimmune hepatitis. It occurred on Day 843 after 28 doses of DAC HYP. Tizanidine was a confounder factor. See extended narrative below.

Selected narratives with more details for the patients listed above.

Study 201	
201/ 454-019	<p>JAUNDICE. 31 F, reported diarrhea on Day 331, and jaundice on Day 336. She received MP for MS relapse on Day 280-283 and started hydroxyzine and escitalopram on Day 300. She was also on an oral contraceptive. Last dose of DAC was on Day 308 (12 doses, week 44). Monthly liver Labs were unremarkable until Day 336 (week 48 visit) when ALT was 1072 u/L (31xULN), AST was 23xULN and BR 2xULN, leading to drug withdrawal. An abdominal ultrasound showed focal liver disease, with 3 foci in the right liver lobe and a large hemangioma (11 cm) in the caudal segment. A non-targeted liver biopsy done on Day 337 showed “acute hepatic dystrophy” with a relatively pronounced zonal necrosis of 25% to 30% of the hepatocytes in the central venous perfusion area. No evidence of acute hepatitis, CMV or EBV infections. Hepatitis E was not tested. No evidence of cholestasis or iron deposits. Of note, this patient developed jaundice almost 1 month after the last dose of DAC and resolved 2 months later without apparent use of corticosteroids. Eosinophils were increased on Day 390 – 420, but not earlier. <i>In my opinion DAC may have played a role in this case, although both methylprednisolone and escitalopram have been reported to be able to induce liver injury.</i></p>

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201/ 763-004	HEPATITIS TOXIC. 40 F, with slight ALT elevation at screening (1.4 x ULN) and throughout the study with ALT 3.8 xULN on Day 140. Last dose on study 201 was on Day 338 (week 48, dose #13 in study 201). Concomitant treatment included metamizole (an analgesic not approved in the US) starting around Day 200. She received IV MP for MS relapse on Day 344 to 348. On week 52 liver tests were about the same as at screening. Four weeks later, on week 56, a nonSAE of hepatic enzyme increase was reported (Day 391). ALT was 1600 u/L (48xULN), AST was 886 u/L and ALP was 166 (<2xULN). BR was 3x from baseline but <u>within normal</u> range. Patient did not enter study 202. The day hepatic enzyme increased “ended” she was diagnosed with toxic allergic hepatitis (Day 428). Metamizole was stopped on Day 439. Hepatitis resolved on Day 457. There is no mention whether hepatitis serology was done. Of note, this patient developed hepatitis almost 2 months after the last dose of DAC150 and lasted 2 months. There is no description of symptoms associated with the event. Apparently it resolved without corticosteroid treatment. <i>Case is confounded by use of metamizole and recent IV MP for MS relapse.</i>
201/ 763-011	ALT and AST INCREASED. 35 M. Mild ALT elevation (1.2 to 1.8 x ULN between Day 197 and Day 208, after 8 doses of DAC 150). Had oral candidiasis on day 218-235 treated with fluconazole. Had AE of ALT/AST elevation on Day 309 (week 44, dose #12)(ALT 731 u/L [17x ULN], AST 327 u/L [9x ULN]) leading to drug withdrawal. BR normal and close to baseline. Subsequently had MS relapse on Day 323 and he was treated with oral dexamethasone. Hepatitis B and C work up was negative. Resolved after 48 days. <i>Insufficient information for full assessment. No obvious alternative explanations. Unclear if dexamethasone was stopped or tapered. As per Dr. Avigan’s review, this is possibly or probable related to DAC HYP.</i>
Study 301 DECIDE (DAC 150)	
301/110-006	HEPATITIS TOXIC. 38 F. Diagnosed with chemical hepatitis on Day 207 (after 4 doses), leading to drug withdrawal. Allergic to Bactrim and morphine. ALT was modestly elevated (<3x ULN) and AST was <2xULN) with normal BR. Patient had intermittent nausea during the study, along with fatigue, insomnia, pains and cognitive disorder. Treated with omeprazole, gabapentin, carbamazepine, paracetamol, oxycocet, eszopiclone, duloxetine, several of which may cause liver toxicity. Drug was withdrawn, event resolved on Day 251. No bx. No corticosteroids. <i>This case of toxic hepatitis is confounded by other hepatotoxic drugs.</i>
301/453-026	20 F, Drug Induced Liver Injury (unconfounded). ALT and AST were mildly increased at baseline. Baseline med was Eugynon. No other concomitant meds. Last dose of DAC was on Day 57 (3rd dose). From Day 57 to Day 80 reported ALT/AST >5x ULN along with BR elevation <2xULN leading to drug withdrawal. Maximum ALT was 633 u/L (18.62 x ULN) and AST was 465 u/L (13.68 x ULN), on Day 57. Diagnosis of DILI was made on Day 154. BR was normal at all times. Testing was negative for hepatitis A, B, C, and E, CMV, EBV, HSV, VZV, Human herpes virus-6 (HHV-6) and

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	<p>Parvovirus B19. Testing was negative for anti-nuclear antibody (ANA), anti-mitochondrial antibody, anti-smooth muscle antibody, anti-soluble liver antigen (anti-SLA). Anti-liver kidney microsomal-1 (anti-LKM-1) was 1.5 (equivocal, as per (b) (4) reference labs). A drug screen was negative for various possible hepatotoxic drugs. Ceruloplasmin and serum IgE were within normal limits. A hepatologist diagnosed the subject with drug-induced hepatitis. The event appears related to DAC. Event resolved after approx. 3 months. Anti DAC antibody was negative at baseline, but positive on Day 185 (value = 60, no units). Neutralizing AB to DAC was negative.</p> <p><i>This is a case of drug induced liver injury with ALT 18x ULN, after 3 doses of DAC HYP 150. No confounding concomitant medications. Resolved after 3 months off-drug, without apparent corticosteroid treatment.</i></p>
301/604-040	<p>HEPATITIS ACUTE. 31 M. Non-serious lymphadenitis on Day 149, not resolved. Renal colic and lymphopenia reported around day 336. Acute hepatitis reported on Day 394 (after 14 doses of DAC150). Concomitant meds at the time of the event of hepatitis included carbamazepine since Day 320. He did take paracetamol initially but had not been taking it for several months; took gabapentin from Day 126 to 320 and venlafaxine from Day 180 to 350, Cipro from Day 186-197. Metamizole taken Day 337-340. Carbamazepine stopped on Day 394. Mild ALT elevation started on Day 360 (<2x ULN); by Day 392 ALT was 31xULN and BR was 2.6x ULN. Drug Withdrawn. Resolved by Day 435, approximately 1 month after the last dose. Labs showed low lymph count starting on Day 85 (total count 0.88 x10⁹ cells/L or lower) with elevated basophils on Day 435. Hepatitis serology negative. Liver-KidneyMicro-1 Antibody IgG was 2.2 on Day 418. SLA Ab IgG was 2.5 (both equivocal result). Anti DAC antibody was negative through week 48 (Day 342), but positive on Day 435, 526 and 571. Neutralizing ab to DAC was positive on Day 435 only. <i>This patient had lymphadenopathy and lymphopenia since earlier in the trial, followed by hepatitis. The case is confounded by use of carbamazepine, gabapentin, antidepressant and analgesic. No biopsy. Resolved without corticosteroid treatment. Liver autoABs equivocal for AIH. Anti-DAC and neutralizing antibodies were transiently positive. The clinical significance of this antibody profile is unclear. Confounded by carbamazepine and metamizole use. I believe DAC may have played a role in increasing the risk of hepatotoxicity of other drugs.</i></p>
301/624-012	<p>ACUTE HEPATIC FAILURE. 34 F. DILI associated with serious drug eruption (AIH in Diff dx) <i>This case of DILI is likely related to carbamazepine and valproate, however, DAC HYP may have contributed to this event. Dr. Avigan confirmed that this is a Hy's law case. See extended narrative after the table.</i></p>
301/670-024	<p>33 M. PT: Elevated liver enzymes (treated with corticosteroids). After consultation with infectologist, the most likely cause was thought to be autoimmune hepatitis. Symptoms improved on high dose prednisone but liver enzymes were slow to come down. On Day 856 treated with oral cephalexin (until Day 862), patient improved. <i>HAC considered a case of infectious cholangitis. In my opinion this could be DAC induced liver injury with hepatocellular</i></p>

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	<i>and obstructive component. See extended narrative after the table.</i>
301/ 670-035	<p>HEPATITIS TOXIC. 28 M. Autoimmune hepatitis as per consultant hepatologist. Last dose of DAC was on Day 447. ALT elevation reported on Day 475. ALT 25x ULN, AST 13x ULN & normal BR almost 2 months after last dose of DAC. ALT normalized by Day 575 but rose again to 14xULN on Day 696 and normalized by Day 772. Concomitant meds were tocopherol and folate. Auto ab panel: Anti-Smooth ab intermittently 1:20 on Day 489 and 685; anti LKM-1 ab between 1.9 and 2.7 (equivocal as per (b) (4)) on Days 507 to 744; SLA ab, IgG 1.5 – 1.8 (equivocal as per (b) (4)) on Days 489 to 744. IgE level increased on Day 521. Intermittent trace protein in urine throughout the study. Bx= acute and chronic hepatitis with mild fibrosis and pericentral necrosis, prob toxic etiology. Suggestion of two possible infections based on serology (HSV and VZV IgM high on Day 685) around the second ALT peak. Improved off drug and with corticosteroid treatment. Patient was Anti-DAC antibody negative throughout the study. Course of liver enzymes for this patient are shown below</p>
	<div style="display: flex; align-items: flex-start;"> <div style="flex: 1;"> </div> <div style="flex: 1; padding-left: 20px;"> <p>301/670-035 <i>As of October 2015, this case was "NOT RESOLVED." Unclear whether patient is still on prednisone.</i></p> </div> </div>
Study extensions	
203/ 453-010	<p>ALT ELEVATION and skin rash (<i>clinical hepatitis after starting valproate</i>) 38 F. Treated with DAC HYP 150. Event occurred after 41 doses in study 203 (Total of 67 doses). Personal and family history of alcohol abuse. In 202 had non-SAE of depression and diarrhea. In 203 had non-SAE of bronchitis, MS relapse and breast abscess and a SAE of severe depression with suicide attempt on Day 1159 of study 203 (benzodiazepines and alcohol). No further doses of DAC HYP were administered. <u>Valproate treatment was started.</u> One month and ½ later, she had increased liver enzymes. Event was associated with fatigue, low grade fever, dark red exanthema, icterus and macula with hemorrhagic base on the lower legs. Liver enzyme elevation led to drug</p>

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	<p>WD. ALTMeds at time of the event included sertraline and clonazepam. The skin lesion was coded as “psoriasis vulgaris”. Viral hepatitis and autoimmune panel was negative. Liver US showed enlarged liver without focal changes, gallbladder without lithiasis. Treatment included MP, prednisone, silybum, betamethasone, Essentiale forte and glucose infusion. <i>This case of symptomatic toxic hepatitis and skin reaction is likely related to the recent addition of valproate. However, DAC HYP may have played a role.</i></p>
<p>203/ 508-012*</p>	<p>HEPATITIS/AIH (Biopsy= pericentral necrosis, lymphoid cells and isolated eosinoph). 43 F. Use of NSAIDs and recent IV MP therapy had elevated liver enzymes after 29 doses of DAC 150 after blinded therapy in base studies (as per datasets: 13 placebo in study 201, 13 DAC 300 in 202). ALT 12xULN, AST 7xULN, normal BR (b) (6) Abd US showed liver steatosis. Drug withdrawn in October 2014. Core needle Liver bx done (b) (6) showed autoimmune hepatitis characterized by numerous and large foci of pericentral necrosis of hepatocytes, inflammatory infiltration of lymphoid cells and isolated eosinophils in the sinuses, the stroma of the periportal spaces, and in the intralobular area. Signs of cholestasis are also present. The picture is one of significant liver damage showing signs suggesting toxic (drug-induced?) changes and then chronic inflammatory damage of this organ. Patient was treated with immunosuppressive regimen and prednisone has been tapered. As per FU on November 2015, the last dose of study drug was 28 Aug 2014 and was not re-started. No further diagnostics were performed. Daily prednisone dosing was 10mg from 28Jul-04 Sep 2015, 8 mg 05 Sep-21 Sep 2015, 5 mg from 22 Sep 2015 with ongoing dosing. The event is ongoing, however improving. Consistent with AIH, with hepatocellular and cholestatic component. <i>Not a Hy’s law case because BR stayed below 2xULN.</i></p>
<p>203/ 512-013*</p>	<p>LIVER ENZYME ELEVATION. 51 M. Hospitalized for workup of liver enzyme abnormality after 31 doses of DAC in extension study and 3 years of blinded therapy in base study. Approx. 2 years and 7 months on DAC. Prior use of amoxicillin for viral infection. Viral serology and autoantibody negative. Drug suspended Dec 2014. On Jan 2015 drug was re-started. Drug permanently discontinued because of second occurrence of LFT elevation (<u>POSITIVE RECHALLENGE</u>). Normal BR. Liver enzymes normalized after DAC discontinuation.</p>
<p>203/ 508-016</p>	<p>HEPATITIS after ampicillin; also had macular rash prior to liver enzyme elevation. 43 F. She received placebo and had cholelithiasis in study 201. She received DAC 150 in study 202 and 203. She had cholecystectomy in study 202. Allergic dermatitis reported in (b) (6) after 32 doses of DAC, with very inflammatory <u>macular lesions</u> on both hands and legs, treated with topical prednisone. DAC was continued. Presented LFT elevation after receiving 39 doses of DAC (b) (6) She had pharyngitis on (b) (6) treated with anti-inflammatory and amoxicillin. Liver US on Day 1093 showed homogeneous and normal size liver with focal lesions. On (b) (6) (study Day 1100) ALT was 9x ULN and AST was 6x ULN. <u>BR not mentioned.</u> Hepatitis dx on the same day which led to drug withdrawal and</p>

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	study discontinuation. She was hospitalized. Potential hepatotoxic meds were discontinued. Event resolved on Day 1571. <i>Skin and liver toxicity probably related to amoxicillin use, but DAC HYP may have contributed to the event.</i>
303/ 543-010*	LIVER ENZYME ELEVATION. Jaundice. 43 F. med hx pleuritic chest pain and ALT elevation. IND 15-day Safety report. At time of event she had tenosynovitis conc. meds were robaxin and diclofenac for unknown duration. She received 35 doses of DAC in 301 and started rx in 303 on Jan 9 2014. Since then, 17 months, most recent dose in May 28 2015. In (b) (6) she was hospitalized with liver enzyme elevation. Had fever for a week followed by icterus and vomiting. ALT and ALT above 6000, BR 45 mmol (normal 21). Did not know if still taking med for tenosynovitis. On (b) (6) alt had returned to 41. She was getting adamethionin and other protective agents. Hepatitis A, B, C and E were negative. Drug discontinued (b) (6) <i>Need to know timing of diclofenac therapy. FOLLOW UP has been REQUESTED.</i>
202/ 765-003	CHRONIC HEPATITIS (DAC 300). 27 F. Chronic and thyrotoxic drug induced hepatitis (after 25 doses of DAC 300). Mild ALT/AST/BR elevation at screening (<2xULN; ALT 57 U/L, nl up to 34; AST 42, nl up to 34, BR 30 mmol/L (normal up to 21). Autoimmune thyroiditis was diagnosed in study 201. She developed hyperthyroidism in study 202, after a total of 20 doses of DAC HYP, treated with carbamazole and propylthiouracil (PTU) (eventually required thyroidectomy). Non-SAE of mild hyperBR was reported on 671 since starting DAC, right after completing carbamazole treatment and approximately 2 weeks into PTU treatment; non-SAEs of ALP, ALT and AST elevation were reported on Day 727 since starting DAC HYP (this was the day of last dose of DAC HYP). On Day 771, at time of hospitalization for thyrotoxicosis she was diagnosed with <u>drug induced hepatitis</u> . Chronic hepatitis was reported as a non-SAE from Days 749-771, and as a SAE from Days 771-910 since starting DAC HYP. No biopsy was done. She was treated with methylprednisolone and oral prednisolone for unknown duration. <i>Before entering 201 the patient had mildly increased liver enzymes, which conceivable may have been caused by unknown, undiagnosed chronic immune hepatitis. Chronic AIH may have been exacerbated by PTU and carbamazole, known hepatotoxic drugs. The role of DAC HYP is unclear. It may have facilitated an uncontrolled autoimmune response. Event of hepatitis is reported as resolved but treatment with oral prednisolone was ongoing at the time of last follow up.</i>
302/ 512-103*	LIVER ENZYME ELEVATION. M of unknown age, started dosing (b) (6), end dosing (b) (6) ALT and AST 10x ULN on Day 225. BR 1.1xULN at start. Resolved around Day 250. <i>As per the HAC report patient did fulfill Hy's law range after the cutoff date of the analyses but it was confounded by Gilbert's and alcohol. Unclear if he received one or two doses of DAC HYP.</i> Associated with ALT increase, acarodermatitis, immunoglobulin E increased, convulsion, monocytosis, sinus bradycardia, otitis media with tympanic perforation, pruritus and maculopapular rash. BR and LFT abnormal from the beginning of trial. Had episode of convulsion and loss of consciousness around Day 80. WD

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	because of AEs. NEEDS FOLLOW UP.
302/ 662-103	<p>AUTOIMMUNE HEPATITIS. (Bx: lymphocytic infiltrate; diffuse chronic hepatitis and fibrosis) 41 F, AIH after 5 doses of DAC HYP 150 in study 302. Led to drug WD. End date on Day 311 (duration 193 days). Med Hx of hyperprolactinemia, Hashimoto's thyroiditis, arthralgia. First event of ALT >5xULN was on study Day 119, the same day of her dose #5. Concom meds at that time were metoprolol, thyroxine, lamotrigine, amantadine and tramadol; she had received IV MP 3 weeks prior to this event. On that day, ALT was 16.2xULN an, AST 8.4xULN with normal BR. A diagnosis of AIH was made a week later (b) (6) ALT peaked to 19.5x ULN, with normal BR. Drug was discontinued. Hepatitis serology was negative; liver US was normal. Autoantibody panel was negative. Lamotrigine was discontinued one month later. A diagnosis of hepatitis toxic was made (b) (6) considered resolved (b) (6) At that time she was treated again with MP for MS relapse. In (b) (6) she again had ALT elevation 4xULN and nausea. CMV testing showed positive IgM serology (from prior negative result; IgG was positive both times), but CMV PCR was negative. Testing for viral hepatitis was negative. Anti-smooth muscle antibody was 1:40. Other liver autoantibodies were negative. He was hospitalized (b) (6) for workup of hepatitis. CT of the abdomen showed signs of cholestasis with no obvious duct gallstone disease and an enlarged lymph node between the pancreas and portal vein. Retroperitoneal lymph nodes were up to 6 mm. On (b) (6) ALT was 16xULN, subsequently he had face edema and abdominal pain. On (b) (6) total BR was 2xULN. She was hospitalized again (b) (6) Liver bx showed liver damage with suspicion of autoimmune inflammation (lymphocytic inflammatory infiltrate in the portal areas; portal fibrosis with connective tissue projections; cytoplasmic ballooning degeneration of hepatocytes. The overall conclusion was diffuse chronic hepatitis with fibrosis grade II/III. Since (b) (6) she also had fever, RUQ pain and dry cough. The patient was admitted again to the hospital for initiation of immunosuppressive therapy with azathioprine and prednisone which started (b) (6) She was discharged (b) (6) in good general condition; face and peripheral edema were resolved; ALT returned to normal by January 10, 2013 and event was considered resolved. <i>I do believe that DAC may have played a role in this case of hepatotoxicity. It is unclear if this patient was able to get off prednisone and azathioprine. As of last followup in July 2015 she was still on 100 mg of azathioprine a day. The patient discontinued the trial and there is no further follow up.</i></p>
303/ 680-001	<p>HEPATITIS TOXIC. 45 M. Toxic hepatitis/ acute hepatic cytolysis 2nd to treatment. Also had hypertensive cardiomyopathy. Received 36 doses in 301 and 2 more doses in 303. A month after the last dose he had chills, sore throat and symptoms of mild MS treated with APAP x 1 day. The following day hospitalized with hepatitis toxic. ALT (6.5 x ULN), AST (2.00 x ULN), elevated ALP, GGT, and LDH (<2xULN). Total bilirubin was within normal limits. Drug</p>

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	withdrawn. Enlarged submandibular nodes , no fever. Hepatomegaly painful to palpation. As per GI consult: gallbladder stones and acute hepatic cytolysis, probably secondary to therapy. Abdominal US showed dilatation of the intrahepatic bile ducts and microlithiasis. <i>Clinical picture appears to be a viral process but serology was negative; there was microlithiasis but consultant thought this was consistent with DILI. He could also have elevated liver enzymes because of cardiomyopathy.</i>
303/ 543-010 *	LIVER ENZYME ELEVATION. 43 F med hx pleuritic chest pain and ALT elevation. IND 15-day Safety report. At time of event she had tenosynovitis conc. meds were robaxin and diclofenac for unknown duration. She received 35 doses of DAC in 301 and started rx in 303 on Jan 9 2014. Since then, 17 months, most recent dose in May 28 2015. In (b) (6) she was hospitalized with liver enzyme elevation. Had fever for a week followed by icterus and vomiting. ALT and ALT above 6000, BR 45 mmol (normal 21). Did not know if still taking med for tenosynovitis. On (b) (6) alt had returned to 41. She was getting ademetionine and other protective agents. Hepatitis A, B, C and E were negative. Drug discontinued (b) (6) <i>Applicant to clarify timing of diclofenac therapy. NEEDS FU.</i>
303/ 649-009	JAUNDICE/ AUTOIMMUNE HEPATITIS. See narrative after the table.

Extended narratives of selected cases

301 624-012. 34 F. “Acute hepatic failure.” DILI. Drug induced hepatitis confounded by carbamazepine use. Probably Hy’s Law case as per HAC. 34 F started treatment with DAC HYP 150 mg in study 301, on (b) (6) (Day 1). On Day 32 she had a seizure and MS relapse (not treated with IV MP). On Day 113 the subject started treatment with carbamazepine for a **focal partial seizure and MS relapse. On the same day a non-serious erythema was noted at the site of** the DAC injection. She saw a dermatologist on Day 120. The rash was described as localized, circumscribed cutaneous event on R arm. On Day 124 she had non-serious papular exanthematous rash. She saw a dermatologist on Day 127. The rash was described as maculopapular eruption on arms, legs and trEMPTY, highly inflammatory with worsening/progression over time. Carbamazepine was discontinued and valproic acid was started for treatment of seizures on Day 127. On Day 127 she also initiated treatment with Herbalife supplement. The rash was treated with topical dexamethasone (Days 127-132), IV hydrocortisone (Days 127 – 131 and 218 to 224) and oral levocetirizine (same days as IV hydrocortisone). On Day 143 she received the 5th DAC dose. On that day, swelling and erythema were noted at the injection site. On Day 169 she received her 6th dose of DAC. ALT was 44 u/L (1.3 xULN) and AST was 37 u/L (1.1x ULN), with normal BR and Alk Phos. She developed swelling on erythematous base approx. 6 hours after injection of DAC-HYP that lasted 3 days. On Day 177 presented nausea, abdominal discomfort consistent with UTI which was treated with ciprofloxacin. On **Day 197** she had

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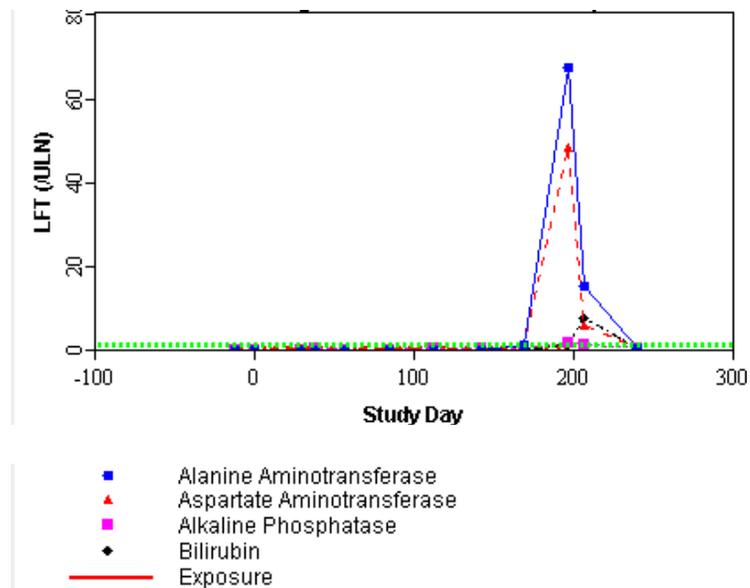
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ALT of 67x ULN, AST 48x ULN and total BR 1.6x ULN and was hospitalized with jaundice. BR peaked at 7x ULN on Day 207. She had elevated INR, decreased level of albumin, and tendency to hypoglycemia. She was diagnosed with **drug induced acute hepatic failure**. She also had a rash from Day 208 to 224. Valproate and other drugs were discontinued on Day 200. Other concomitant medications included paracetamol throughout the study for prophylaxis of Avonex (placebo) flu-like symptoms, sertraline since day 32, Cipro for UTI; while hospitalized with diagnosis of liver failure she received, plasma, glucose and urodeoxycolic acid.

A liver biopsy showed marked **centrilobular and bridging necrosis** with hepatocellular regeneration and hepatocellular ballooning; scattered lymphoid cells and acidophilic bodies were present in the lobules; macrophages in the necrotic areas contained pigment (bile); the portal tracts were expanded and showed a mild to moderate infiltrate of **lymphoid cells admixed with some neutrophils and eosinophils**; bile duct damage and ductular reaction were noted; and viral inclusions were not identified. Overall, the findings in the biopsy were most consistent with **drug-induced hepatic injury**. Other conditions, such as (*spontaneous*) autoimmune hepatitis and viral hepatitis were considered less likely but could not be excluded.

Liver related labs are shown below (generated with Empirica Study).



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Testing on Day 207 was negative for hepatitis A, B, and C and E. Testing for EBV, CMV and VZV was consistent with past infection. Testing for Herpes simplex virus (HSV) ½ IgM was positive but IFA confirmation was negative. Testing for Human herpes virus -6 (HHV-6) and Parvovirus B19 was negative. ANA and AMA were negative. Anti Smooth muscle (ASMA) antibody was 1:40. Anti DAC antibody was negative at all times. The patient gradually improved and event was considered resolved by Day 241.

This is a case of severe drug induced liver injury with full blown acute liver failure (prolonged INR, hypoglycemia) and extensive rash in a patient taking DAC HYP 150, confounded by use of potentially hepatotoxic medications commonly used in patients with MS (carbamazepine for 10 days, followed by valproate for approx. 2 months). A positive ASM antibody is typically associated with autoimmune hepatitis but a titer of 1:40 is undetermined (in adults, titers of 1:80 or higher are considered specific of autoimmune hepatitis; in children, titers of 1:20 are considered positive).(UPTODATE). As per the HAC, this was a Probable Hy's Law case (>50% likelihood of being related to daclizumab).

It is interesting that the day she started carbamazepine she had a local reaction to the daclizumab injection. A local reaction continued to occur every time she received DAC, on Day 143 and Day 169. Liver Bx with mixed hepatocellular and cholestatic damage and eosinophils. Liver failure occurred more than 2 months after the last dose of carbamazepine, while on valproate.

*As per the narrative the patient had received 7 doses before the event and the most recent dose was on Day 169; as per the patient profile, the last dose was on (b) (6) Day 197. **As per a response for clarification submitted on July 2015, the patient indeed received the last dose of DAC on Day 197. This event occurred after the protocol amendments that emphasized that investigators had to see the labs before the next dosing (b) (6) and underscore how difficult it may be to monitor these patient in the postmarketing setting.***

301/670 024. PT: Elevated liver enzymes (treated with corticosteroids).

Medical hx low folic acid levels. Started DAC in Feb 2010. Hepatic Labs normal until March 11 2014. In March 31, 2014 during routine labs ALT was 1332 U/L (ref 6-43), AST 726 U/L (ref 11-36) GGT 895 U/L (ref 10-61) total BR 53 umol/L (ref 33-55), ALK P 485 (ref 31-129). This is inconsistent with other sentence in the IND report: "On 31 Mar 2014, the subject's TBIL was elevated for the first time at 3.1 mg/dL (> 2.5 times upper limit of normal (ULN); central lab ref range 0.2-1.2). On 04 Apr 2014, TBIL increased to 5.0 mg/dL (> four times ULN) (per central labs; ref range different). "ON (b) (6) at the clinic ALT 969, AST 478, Total BR 74. As per (b) (4)

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labs: ALT 1126, AST 526, TB 86, ALP 617 (ref 42-141). Subject reported fatigue, low appetite, dark urine and jaundice. He was

hospitalized for elevated liver enzymes. No report of abdominal pain. **After consultation with infectologist, the most likely cause was autoimmune hepatitis.** The total number of DAC doses received was 27 with last dose given in JANUARY 2014. On (b) (6)

(b) (6) abdominal ultrasound showed normal findings on the liver and an enlarged **lymph node 2 cm in diameter next to the head of the pancreas**. Spleen was slightly enlarged. Serology for Hepatitis and other viral etiologies was negative. ANA, AMA and liver autoantibody panel and drug screen was negative. Lab test (b) (6) showed WBC 6.8×10^9 , neutrophils 56%, lymphs 27%, monocytes 5.6%, eosinophils 9.8%. ESR 3 mm/h, CRP 7.9 mg/L (0-5), Fibrinogen 2.4 g/L (2.2-4.9) Total Bili 101 umol/L (3-21)), Direct BR 75.4 (0.1-8.6), ALT 819 U/L (5-40), ALP 721 U/L (30-115) GGT 1246 U/L (1-55). Total protein 65 g/L, Albumin 42.7. PT/APTT normal. Corticosteroids were begun (b) (6) (Prednisone 60 mg daily). Abdominal ultrasound showed normal findings on the liver and an enlarged **lymph node 2 cm in diameter next to the head of the pancreas**. Spleen was slightly enlarged. Fatigue improved, appetite was better and jaundice was less prominent after starting high dose prednisone. However, the response was considered to be slow, and other etiologic factors could not be ruled out. On (b) (6) WBC 10.7, neutrophils 65%, Lymphs 25.5%, monocytes 6.3%, Eos 2.3%. ESR 4 mm/h, CRP 5.2 mg/L, TBR 72 umol/L, Direct BR 53.8, ALT 785, AST 457, GGT 1502, ALP 862. On (b) (6) Ferritin 1057 ug/L (10-120); normal iron and transferrin levels. TBR 62 umol/L, Direct BR 44 umol/L, ALT 606, AST 240, GGT 1656, ALP 926. On (b) (6) lab tests: ALP 831 U/L, ALT 531 U/L, AST 188 U/L, GGT 1441 U/L, direct bili 1.8 mg/dL, indirect bili 1.3 mg/dL; total bili 3.1 mg/dL. (b) (6) - (b) (4) ALT 477 U/L, AST 184 U/L, GGT 1368 U/L, TBIL 50 umol/L, AMY 53 U/L; ALP 685 U/L. On (b) (6) subject showed no signs of symptoms of liver disease and was feeling well.

On (b) (6) MRI cholangiopancreatography and abdominal MRI showed normal results for liver, gallbladder, extrahepatic bile ducts, pancreas, spleen, kidneys, abdominal aorta and VCI, and other intraperitoneal and retroperitoneal lymph nodes. **The intrahepatic bile ducts showed mild segmental narrowing of the lumen and mild narrowing in the region of the papilla.** Small segmented bile ducts were not displayed, possibly in the context of cholangitis lesions. In the region of the hepatic hilum mild enlargement of single lymph node was noted, showing a diameter of approximately 16 mm. No pathologic fluid accumulation in the pleural space was registered. The possibility of bile duct inflammation was diagnosed. MRI concluded suspected cholangitis with reactive single lymph node enlargement in the hilar region of the liver. Therefore antibiotic treatment with cefalexin and pipemidic acid were started. Antibiotic therapy was introduced (b) (6) followed by rapid improvement of lab values. (b) (6) WBC 15.2, neutrophils 66%, lymphs 29%, monos 3%, eos 2%. CRP 1.8mg/L, TBili 28 umol/L, Direct BR 17.6, ALT 174 U/L, AST 35, GGT 944. (b) (6): wbc 9.9×10^9 , TBR 23 umol/L., Direct BR 13.4, ALT 55 U/L, AST 21 U/L, GGT 477 U/L, ALP 269 U/L.

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Dr. Mark Avigan concurs with the Hepatic Adjudication Committee that his was bacterial cholangitis. I concur with a diagnosis of cholangitis but I think this could be DAC induced DILI with an hepatocellular and obstructive (cholangitic) component.

302/622-103. PT: Autoimmune hepatitis. This is a 41 year-old female who developed AIH after 5 doses of DAC 150. Last dose was (b) (6). On that date, at Week 16, the subject presented with an elevated ALT of 551 U/L, AST of 286 U/L and total BR was 15 umol/L (within normal). Two days later the ALT was 663 U/L and the AST was 326 U/L and total BR was 22 umol/L. The subject was treated with ursodeoxycholic acid. The patient had received MP for an MS relapse about 3 weeks before the last dose, (b) (6). She was asymptomatic. Liver US was normal. Lamotrigine discontinued August 2012. Dx of Hepatitis toxic made (b) (6). ALT improved and resolved (b) (6). On (b) (6) the subject again experienced an increase in ALT to 146 U/L and AST at 130 U/L. The subject complained of nausea. Laboratory testing was significant for a change in the CMV IgM serology from negative (b) (6) to positive (b) (6). CMV IgG was positive at both time points (b) (6). A CMV PCR test was negative (b) (6). The biopsy was consistent with diffuse **chronic hepatitis with fibrosis grade II/III consistent with autoimmune hepatitis.** ("The bile ductules structure is WNL. There is portal fibrosis with connective tissue projections. Porto-portal connective tissue bridges are found. In single hepatocytes, cytoplasmic ballooning degeneration is visible. No steatosis, cholestasis or focal hepatocyte necrosis"). On (b) (6) the subject was re-hospitalized for observation and **initiation of immunosuppressive therapy for autoimmune hepatitis** following histopathological biopsy diagnosis. During hospitalization (b) (6) the subject was treated with azathioprine (50 mg/day) and prednisone. The prednisone dose was 40 mg/day with a planned gradual dose reduction to 10 mg/day. LFTs resolved (b) (6). As per a response to an FDA request, the patient is still on low dose prednisone and AZA.

303/649-009. 46 F. Jaundice. Investigator later changed Dx to **Autoimmune Hepatitis** based on biopsy results. The patient received IFNβ1a during study 301. Liver enzymes were within normal values throughout study 301. She was diagnosed with hypothyroidism and started levothyroxine on Day 946 of study 301. She also was diagnosis with hypophyseal adenoma in 301. At the time of the 4th dose of DAC in study 303, on (b) (6) (4th dose) her ALT was slightly elevated at 58 U/L (6-34 U/L). ALT measured before the 5th dose (b) (6) was 766 U/L with normal BR therefore dose was not given. Treatment was withdrawn. (b) (6) hospitalized with **jaundice**, fatigue, dark urine, light feces. ALT 863, AST 1003, GGT 225, TBI 148.8 umol/L with direct bilirubin of 98.9 umol/L, alkaline phosphatase of 208 U/L and GGT of 225 U/L. Palpable liver. Extensive serology for current viral infections was negative. Testing for ANA was elevated at 1:160 (homogenous pattern), liver specific auto antibodies anti-LKM1 Ab, antimitochondrial Ab, anti-SLA Ab, and anti-SMA Ab were negative. The subject was seen by a gastroenterologist/ hepatologist who gave the diagnosis of **severe toxic drug induced hepatitis with distinct cytolysis syndrome** and the subject was treated with MP IV 1000 mg for 5 days (started (b) (6)). At that time, (b) (6) ALT was 736 U/L, AST was 698 U/L, total bilirubin was 5.1

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mg/dL (direct bilirubin 2.8 mg/dL), alkaline phosphatase was 185 U/L and GGT was 184 U/L. After pulse steroids the subject began a taper of **120mg Prednisolone (2 days), 100 mg Prednisolone (b) (6) (2 days) with further taper** to 80mg (2 days). The hepatologist did not recommend a liver biopsy at this time as the subject was continuing to improve. MP taper was planned. As of (b) (6) (b) (6) LFTs were continuing to improve and she was discharged from the hospital. ALT was 144 U/L, AST 60 U/L, Total bili 1.7mg/dL, and GGT was 127 U/L. On (b) (6) a diagnosis of chronic glomerulonephritis was made based on abdominal US (“queries pending”). Creatinine and BUN normal throughout study 301 and 303. ALT and BR normalized (b) (6) On (b) (6), thrombocytopenia was reported after the patient was off prednisone (after cut-off of SUR), requiring a second course of corticosteroids. As per a response to an FDA request for follow up, the thrombocytopenia was successfully treated with corticosteroids and is currently off steroids.

This patient developed hypothyroidism during IFNβ1a treatment. Four months into DAC HYP treatment she was diagnosed by hepatologist with drug induced hepatitis with jaundice. Later she had a questionable diagnosis of chronic glomerulonephritis (not confirmed) and a diagnosis of thrombocytopenia (after cut-off date of the SUR). As per the HAC discussions this might have represented drug induced autoimmune hepatitis versus spontaneous autoimmune hepatitis in a patient with propensity to autoimmunity. I agree that she may have some predisposition to autoimmunity but there was no evidence of hepatitis or thrombocytopenia before she received DAC.

This is the second case of thyroid disease and autoimmune hepatitis in a patient on DACAs per the applicant’s response to FDA request, the diagnosis of glomerulonephritis was never confirmed.

13.3.4.3 Listings and selected narratives non-serious AE leading to drug withdrawal in the Hepatobiliary or Investigations SOCs

ID	PT	Comments
Study 201 (on DAC 150)		
304-006	HEPATIC ENZYME INCREASED 49 F. Received 12 doses of DAC HYP. Last dose on Day 308. <i>Mild increase in liver enzymes leading to drug WD; skin rash complicated with fatal infection. It is unclear whether the liver toxicity and skin rash were related.</i>	
460-010	HEPATIC ENZYME INCREASED 23 F. Received 6 doses of DAC. “Viral infection” on Day 57-60 treated with ibuprofen. Had MS relapse on Day 62-86	

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	treated with IV MP. Amantadine Days 86-243. Omeprazole Day64-66. ALT was <1.5 ULN at entry and up to Day 32. On Day 109 ALT 4x ULN. AE Hepatic enzyme increase reported on Day 142 to 393 led to WD. Last dose of DAC was on Day 141 (6 th dose). On Day 175, ALT 20x ULN; AST 10x ULN. Normal BR and ALK P. ALT/AST normalized by Day 340 (6 months after last dose).
Study 301 (on DAC 150)	
205-006	<p>AST/ALT INCREASED</p> <p>33 F. Hx of hypothyroidism on levothyroxine. ALT and AST increased 3xULN after 16 doses of DAC, Day420. Patient was taking paracetamol. Paracetamol stopped Day 443 ALT normal by Day 466. ALT and AST increased again. On Day 527 ALT was 1.4xULN. Last dose was given on Day 561 (dose #21). ALT peaked on Day 583 (50x ULN) with AST 20xULN and BR 1.5xULN (10x from baseline); ALP also mild elevation. No concomitant meds at the time. Labs showed increased platelets, thyroxin, IgE and Alpha1 Globulin/Total protein. Allergic dermatitis on Days 696 - 715 treated with oral corticosteroids for 2 weeks. ALT decreased over time down to 2x ULN with AST 1.2xULN on Day 1001. IFN beta started Day 733. DAY 605: ANA positive 1:80; AMA, ASMA negative. LKM-1 Ab IgG 5.4 U, SLA-AB IgG 2.6 U. High IgE. NOT RESOLVED as of the SUR.</p>
228-003	<p>ALT INCREASED</p> <p>34 F. Received 35 doses of DAC. Eczema Day 223-282. Skin induration and erythematous lesions Day 331-346. Severe MS relapse Day 352. Irregular menstrual bleeding. Bleeding at IFNβ1a placebo injection site Day 553 and 665. Contact dermatitis Day 583-639. MS relapse, Day 652. Hypoesthesia Day 685 not resolved. ALT increased Day 702-756 led to drug WD. Last dose Day 672. ALT on Day 709 was 12xULN; AST 5xULN. On Day 724-792: Diffuse Maculopapular rash. Paresthesia and muscular weakness R upper limb Day 756-778. Day 756 rash described as >30% BSA, highly inflammatory worsening over time; treated with IV MP followed by oral prednisolone Days 764 to 783; resolved by Day 792. ANA & AMA negative. LKM-1 ab IgG 1.7. SLA Ab IgG 1.7U. ASMA 1:20. Hepatitis, EBV, CMV, VZV, Parvovirus negative.</p>
254-007	<p>HEPATIC ENZYME INCREASED</p> <p>ALT >2xULN on Day 271. Peak ALT on Day 300 (14xULN) AST >5xULN, normal ALK P and BR. Patient taking paracetamol. Had MS relapse treated with oral MP on Day 197-200. Chlorzoxazone and nimesulide given on Day 249. Paracetamol stopped Day 280. Tocopherol, URSO given Day 300. DILI confounded by paracetamol, chlorzoxazone and nimesulide. Did not fully recover. <i>Last ALT measurement close to 2xULN</i>. NOT RESOLVED as of the SUR.</p>
311-020	<p>LFT ABNORMAL</p> <p>ALT >10xULN after treatment with IV MP for MS relapse on Days 515 to 520. Received 20 doses of DAC. Diffuse maculopapular eruption Day 448 In neck and trunk. ALT 10x ULN , AST 5x ULN on Day 560. Peak 15 x ULN Day 574. As per labs, ALT normal by Day 643. ANA 1/160 speckled. LKM1Ab IgG 2 U. SLA Ab IgG 1.6 U. Anti DAC ab negative. Severe ALT elevation, not resolved as of the SUR.</p>

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329-004	<p>LFT ABNORMAL</p> <p>LFT abnormal after 28 doses of DAC (Day 725, no end date). ALT intermittently elevated <2xULN between Days 100-350. Short use of pregabalin, paracetamol, duloxetine, MP (Day 187-190 for MS relapse), nortriptyline Day 209 to 411, amoxicillin Day 447. No other meds around Day 725. Peak ALT 3.5xULN. AST 3xULN, ALK P mild elevation. Last ALT value Day 827 close to normal range. LKM1 Ig 1.9 U. SLA Ig 3.1. Anti Dac ab negative. Not resolved as of the SUR.</p>
451-007	<p>ALT INCREASED</p> <p>54 F. NOT RESOLVED. 3xULN after 4 doses, on Day 93; 5th (last) dose given on Day 126. ALT continued to increase. At time of last FU ALT >6xULN on Day 190. Negative Hepatitis and viral panel. Not resolved as of SUR.</p>
453-041	<p>LFT ABNORMAL</p> <p>39 M. MS relapse Day 128 (no CS given). LFT abnormal Days 199-295. Last dose of DAC Day 198 (8 doses). Peak ALT 18x ULN and AST 11xULN on Day 245. GGT also increased. BR increased 4 fold but was within normal. Treated with oral prednisone Day 286 to 285. <i>Treated with Prednisone 62 mg PO Day 257-286 "for DAC elevated LFT"</i> ALT normal by Day 311. LKM1 ab 1.2 U, SLA Ab 1.6 U. DAC AB negative. <i>As per fu submitted 3/3/16, the AE was reported as resolved on 12 Sep 2012 (DAC Day 297). The event led to the subject's subsequent withdrawal from the study with his last visit occurring on 05 Dec 2012 (DAC Day 381). I doubt that he was treated only for one month. He likely underwent some tapering.</i></p>
541-005	<p>HEPATITIS TOXIC</p> <p>26 M. Patient had allergic dermatitis over the shoulders on unknown date during study 301 in August 2013, treated with mometasone, that resolved. In December 2013 (Day 932) AE of "Cryptogenic hepatitis, probably toxic" was reported. No conc meds. He had received 32 doses of DAC. Last dose was on Day 870. Peak ALT was 3xULN on Day 913. BR normal. DAC AB negative. <i>No workup reported. Event reported as resolved on Day 1067. He was withdrawn from the study. Treated with URSO.</i></p>
554-017	<p>ALT/AST INCREASED</p> <p>38 F. ALT/AST increased Days 673 to 767, after 26 doses. Last dose Day 673. ALT peak Day 700, 5xULN. Three MS relapses, leukopenia, anemia (Day 392-845), second and third MS relapse treated with IV MP (Days 439 to 447 and Day 593 to 599). Omeprazole Day 595-599. APAP given Days 553-668. Cytoflavin (psychostimulant) Day 653-669. ALT increased right after these meds. ALT resolved by Day 847. Started IFN on Day 827. Viral panel negative except VZV IgG and IgM high Day 701. ANA, AMA, ASMA negative. LKM1 ab 3.6 U., SLA ab IgG 2.5U. Anti DAC ab negative.</p>
592-001	<p>ALT/AST INCREASED</p> <p>44 F. Last dose of DAC in study 301 (#13) was on Day 336. AE reported Day 365. At that time patient was on baclofen, ketoprofen and pantoprazole. All three were discontinued when ALT elevated. Sudden increase of ALT, from normal on Day 337 to 50x ULN on Day 364. ALT down to 2.5xULN on Day 397 but up to 32xULN on</p>

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	<p>Day 404. BR 1.2xULN on Day 404 (but increased 3x from baseline). Consent withdrawn. VZV IgG and IgM positive on Day 410. Reported end date was Day 457. <i>Confounded by concomitant meds and possible VZV infection. Low albumin. Antibody panel negative.</i></p>
611-042	<p>BLOOD BR INCREASED 47 F. Increased BR since baseline, normal ALT/AST. Probably had Gilbert's. WD after 7 doses for BR increased on Day 172, considered "severe". Hepatitis panel negative. No autoantibody panel. DAC ab negative. Not resolved as of SUR.</p>
611-048	<p>LFT ABNORMAL 49 F. WD after 23 doses. Last dose on Day 617. Lip exfoliation Day 559 to 617; LFT abnormal Day 655 to 674; cheilitis and seborrheic dermatitis Day 708 to 723 treated with topical treatment. Concomitant meds sertraline on Days 590 to 645 and 687-701. Theraflu Day 639-641. Normal liver enzymes on Day 617 Sudden increase on day 645: ALT 31xULN, AST 16xULN. ALK P 174 U/L (normal up to 123 U/L). BR was normal. This patient had both a cutaneous and a liver reaction. ALT normal by Day 729. ANA 1:80, LKM1ablg 2.6U. SLA Ig 2.1 U. Anti DAC neg.</p>
612-004	<p>ALT/AST INCREASED 50 F. ALT AST elevated reported after 30 doses. Sudden increase of ALT from normal on Day 837 to 14xULN on Day 865, AST and GGT also increased, normal BR. Last dose Day 837. Treated with paracetamol, pheniramine, amantadine (Day 265 to 713, carbamazepine (unclear reason), piracetam (329 to 836), venlafaxine Day 329-712. IV MP Days 521, Day 594 and Day 708 for MS relapses (3-5 days each time), gabapentin Days 846-864. End date: Day 995. Confounded by multiple potential drugs. Hepatitis panel negative, ANA, AMA, ASMA negative; LKM1 IgG 3.8 U, SLA ab IgG 1.4 U. Anti DAC ab positive Day 418, 964 and 995. Neutralizing ab positive Day 964 and 995.</p>
614-010	<p>ALT INCREASED 48 F. "severe" ALT increase. ALT 3xULN, AST 5xULN. GGT and ALK P increased before ALT/AST. Last dose on Day 840. Peak ALT/AST Day 869 (ALT 8xULN, AST 5xULN, GGT x10 ULN and ALP 4xULN). Intermittent thrombocytosis. Concom meds: aspirin and timonacic. Hepatitis, autoantibodies and drug screen negative. Intermittent mild increase in BR (prob Gilbert's). ALT/AST resolved Day 890. ALP resolved Day 925. GGT still 2xULN on Day 1009. Not resolved</p>
625-001	<p>ALT INCREASED 48 F. ALT increased reported on Day 807. Confounded. Gabapentin, levothyroxine, levodopa. APAP. Last dose Day 781. ALT up to 4xULN on Day 674, down to normal on Day 753, then up again to 6xULN on Day 807 and 8xULN with AST 5xULN on Day 831. ALT still 5xULN on Day 876. Down to 1.3x ULN on Day 956. No additional follow up. ANA, AMA, ASMA negative; LKM1 Ig 2.2, SLA ab 2.6 U. Not resolved as of SUR.</p>
648-012	<p>LFT ABNORMAL LFT abnormal on Day 673 (severe). No conc. meds at time of event. Last value ALT still 2x ULN. Not resolved as of SUR.</p>

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649-006	<p>ALT INCREASED, AST & blood BR increased 50 F. ALT, AST and BR increased Day 729-799. AST increased led to drug WD. Diagnosed with Biliary dyskinesia. Idiopathic chronic hepatitis. Irritable bowel syndrome. Chronic cholecystitis and cholelithiasis. She was taking diclofenac, ibuprofen and meloxicam during the study (<i>exact start and end date of these NSAIDs not known</i>). Last dose of DAC was Day 701. On that Day ALT was 1.5xULN with normal AST. They increased gradually with peak ALT of 11xULN, AST 6xULN and BR 2.9x ULN on Day 737. Normal ALP. ALT normal by Day 805 but direct and indirect BR persisted slightly elevated. Gilbert's disease suspected. Liver autoAB panel not done. Anti DACab was positive.</p>
667-027	<p>ALT INCREASED 37 M. Received 14 doses of DAC. Last dose Day 362. Elevated ALT/AST on Day 374 led to interruption and then drug WD. IV MP for MS relapse Day 254-258. Other meds: sertraline, Vit B12 and alfacalcidol Days 258-369. Spektramox for sore throat Days 337-346. Influenza vaccine Day 347. ALT initial increase Day 309 (1.4xULN), on Day 362 ALT 6.7xULN, Day 372 ALT 8x ULN, AST 4xULN, Normal BR and ALK P. Enzymes normalized by Day 414. Anti DAC ab positive Day 505.</p>
680-004	<p>HEPATOTOXICITY 44 F. Verbatim: toxicatrogenic hepatopathy, dose initially interrupted but later withdrawn. On day 285 ALT/AST suddenly increased to 2.4 xULN. Day 344 ALT/ALS >3xULN. ALP and BR normal. On Day 384 reported to have "hepatotoxicity" Treatment included an herbal preparation (Liv 52). On Day 365 ALT resolved without stopping DAC. On Day 401 hepatotoxicity recurred ALT 3.3xULN, AST 1.8xULN. Treated with s. marinatum. DAC was permanently WD. HepB core ab was positive on Day 418, but HBSAg and Ab were negative. Hep C was negative. No other special hepatic tests were performed. <i>ALT came to normal but follow up is short and ALT could have increased again.</i> Pt withdrew consent on Day 481. Anti DAC ab negative. Not resolved as of the SUR.</p>
Study 203	
453-018	<p>LIVER DISORDER/hepatopathy 49F. Placebo/150/150. Also had Toxoallergic rash on Day 322-518 of study 203, treated with cetirizine. MS relapse treated with IV MP Day 595 and 674-678. Patient on gabapentin, levothyroxine and ramipril at time of event. Liver disorder Day 730-847 of study 203. ALT elevated 2xULN Day 646, peaked at 4.6xULN on Day 730. AST 1.6xULN same day. As per last visit on Day 925 ALT still >2xULN. Hepatitis and liver ab panel negative. LKM1 3.7; SLA ab 2.7. Ceruloplasm 2520. DAC ab negative. DID NOT RESOLVE</p>
453-021	<p>HEPATIC ENZYME INCREASED 25 F. Received DAC HYP 150 in 201/202/203. Received 26 doses of DAC 150 in 201/202 and 2 doses in 203. Last dose Day 28 of study 203, week 4. (Day 792 of total exposure) "Interrupted" because of SAE of urticaria on Week 8 of study 203, but no further doses given. ALT increase was identified one month later, on Day 62 of study 203, with peak on Day 70 (ALT 17xULN; AST 13xULN). She received doxycycline Day 7-27; levocetirizine and omeprazole day 6-76, and was taking nimesulide for headaches. Lasted several months. Resolved by Day 421 of study 203 (1067 of total dose; event was</p>

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	severe and lasted 276 days). DAC ab was negative in 202 up to week 52; positive at week 24 (Day 163 of study 203) and negative on further testing.
459-004	HEPATIC ENZYME INCREASED 26 F. On DAC 150 in 201/202/203. Days 586-621 of 203 had severe hepatic enzyme increased leading to WD. Peak ALT/AST on Day 593 of study 203 (10x and 5x ULN respectively). Received 26 doses in 201/202 and 21 doses in 203. Last dose on Day 565 . Developed lymphadenopathy in 201/202. Had 4 episodes of MS relapse in 203, between Days 27 and 500. Several episodes of “viral infection”, AE of gastroenteritis (Day 584-591). Days 586-621 hepatic enzyme increased - >WD . <i>First episode of ALT elevation possible related to DAC, confounded by use of IV MP. Second episode on Day 750 probably related to other meds. Low titers of ASMA and LKM1 Ab these are equivocal values for</i> (b) (4)
506-012	ALT INCREASED 150/150/150. On Day 872 to 877 of treatment had moderate ALT increased in patient with ulcerative colitis.
508-010	ALCOHOLIC LIVER DISEASE 43 F. 150/150/150 Alcohol abuse reported Day 96 to 171 of study 203. Alcoholic liver disease and toxic liver injury Day 143-310---> WD. AST&ALT (AST>ALT) GGT and ALP, peaked on Day 225-237. Hep B & C negative. Resolved Day 251. Skin rash noted Day 159. Exfoliative dermatitis Day 282 not resolved, treated with cetirizine and topical rx. Oral prednisone Day 319-343. Anti DAC ab negative.
508-016	HEPATIC LESION 43 F. Placebo/150/150. Hx of Cholelithiasis, migraines, goiter, anemia due to Vit B12 deficiency. Hepatic lesion reported Day 1459 to 1467, of “moderate intensity” Concom meds fluoxetine, levothyroxine, amantadine ferrous sulfate. MS relapse after 9 doses of DAC treated with IV MP. After 10 th DAC dose had biliary colic and underwent elective cholecystectomy. Had toxic hepatitis in 203.
510-001	AST, GGT, ALP, ALT increased 46 M. DAC 300/300/150. Received total of 51 doses of DAC. Last dose day 393 of study 203. Intermittent rash in 202. Diffuse rash in 203 day 258-272. Syncope Day 295. Dexamethasone IV day 363 for rash. Mianserine Day 164-288. Patient on simvastatin and bisoprolol. AE ALP and ALT increased day 421-430, AST, GGT increased Day 421-442 of study 203. ALT 4.8xULN and AST 2.6xULN on Day 421 . Improved. Resolved by day 442 of study 203. <i>Confounded by other meds.</i>
553-005	LIVER DISORDER 22 M. 150/Pla-150/150. “Toxic hepatopathy”. Diagnosed as Sertraline liver toxicity, however, data of sertraline use is unclear. <i>DNP unable to get date of sertraline dosing despite repeated request to applicant.</i>
763-020	ALT INCREASED 36F. Patient received DAC 300 in 201/Pla-300 in 202 and DAC150 in 203. Total of 29 doses of DAC. AE ALT increased on Day 910 to of moderate intensity. Had ongoing chronic pancreatitis and pyelonephritis. Last dose Day 225 in 203 . ALT

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	elevation Day90. Chronic cholecystitis Day 100. ALTx5xULN Day 181 -> WD. Improved. LABS Day 195: ANA 1:80, speckled/homogeneous, LKM1 ab IgG 3.9U. SLA ab 2.6U. <i>Anti DAC ab positive in 201 at week 0= 23.3 (false positive?)</i> Negative at all other times in all 3 studies
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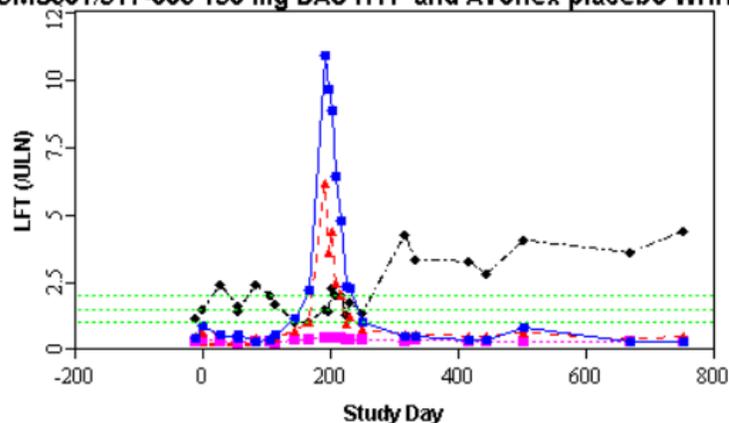
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13.3.4.4 Narrative of patients with liver enzymes in the Hy's law range identified by eDISH plots, not previously discussed.

301/517-003 As per the Empirica Study graphic profile, the patient had elevated BR at baseline. ALT increased to 10x ULN after 4 doses of DAC, confounded by use of paracetamol and IV MP relapse. Patient discontinued drug. Last dose was on Day 85 of the study. The patient fulfilled protocol defined progression of disability on Day 167. Peak ALT was on Day 196 (ALT= 418 U/L). Gilbert's was diagnosed on Day 334. Axillary mass was diagnosed on Day 739. *Although confounded by Gilbert's this case appears to be DILI.*

5MS301/517-003 150 mg DAC HYP and Avonex placebo WHITE M



- Alanine Aminotransferase
- ▲ Aspartate Aminotransferase
- Alkaline Phosphatase
- ◆ Bilirubin

301/611-007 26 M. Presented presyncope after the second dose of DAC. Also reported asthenia. Events resolved. Liver function test abnormal reported on Day 672 to 701, after 23 doses of DAC. Drug interrupted but continued and received 11 more doses. Completed the study. No concomitant medications at the time of ALT elevation. He had elevated BR from the start of the trial,

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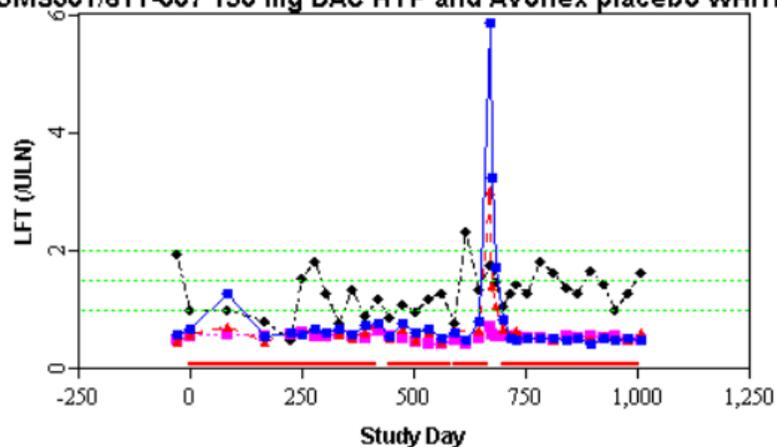
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suggestive of Gilbert's. *This is the only case I have identified in the entire DAC database, in which ALT >5xULN decreases without drug discontinuation.*

5MS301/611-007 150 mg DAC HYP and Avonex placebo WHITE M



- Alanine Aminotransferase
- ▲ Aspartate Aminotransferase
- Alkaline Phosphatase
- ◆ Bilirubin
- Exposure

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13.3.4.5 CASES IN WHICH ACTION TAKEN WITH DRUG IS ‘INTERRUPTED’, but patient discontinued drug treatment

A total of 90 patients had AE that led to treatment interruption in Hepatobiliary SOC and Investigations SOC/HB HLG T as of the SUR (ADA E3 dataset, submitted 6/25/15). Of those 90, 12 actually withdrew treatment (either before, at the same time or later). These patients are listed below.

ID
203/506-011
203/553-006
203/559-002
203/758-006
203/759-008
203/902-003
301/110-002
301/541-005
301/554-017
301/649-006
301/667-027
302/622-108
303/670-036

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13.3.4.6 Cases referred by the applicant to the Hepatic Adjudication Committee (HAC)

The applicant conveyed a panel of hepatologists (b) (4) referred to as the Hepatic Adjudication Committee (HAC) to independently evaluate cases fulfilling Hy's Law biochemical criteria (defined as ALT or AST >3x ULN and total BR >2x ULN) in a blinded fashion in all Daclizumab HYP studies. Additional cases of interest were referred for adjudication at the discretion of the sponsor. The HAC reviewed laboratory values, eDISH displays, and individual cases to determine whether they were true Hy's Law Cases (related to study drug) or whether there were alternative explanations or contributory factors. The report noted that serum ALT or AST >3x ULN and serum total bilirubin >2x ULN do not always represent a serious liver safety signal. Viral hepatitis or passing a gall stone can also cause a patient to experience simultaneous elevations in serum ALT and bilirubin and do not represent Hy's Law cases. A peak serum BR that occurred weeks before the peak serum ALT, would not be consistent with an acute hepatocellular injury causing liver dysfunction (such in cases of Gilbert's syndrome or hemolysis). In addition to ALT and BR values, a condition to consider a case a true Hy's Law Case was that they occurred concurrently, within 30 days of each other. The three hepatologists used the causality assessment scale adopted by the Drug-Induced Liver Injury Network with the addition of an "unassessable" category, as follows

Definite: >95% likelihood. The evidence for the drug causing the injury is beyond a reasonable doubt.

Highly likely: 75%-95% likelihood. The evidence for the drug causing the injury is clear and convincing but not definite.

Probable: 50%-74% likelihood. The preponderance of the evidence supports the link between the drug and the liver injury.

Possible: 25%-49% likelihood. The evidence for the drug causing the injury is equivocal but present.

Unlikely: <25% likelihood. There is evidence that an etiological factor other than a drug caused the injury.

Unassessable: Insufficient information to assess causality.

If no agreement was reached among the three HAC members, the category would be defined by the chair of the committee. The committee reviewed all cases in a blinded fashion and met again after cases were unblinded, along with additional information. During the final adjudication, most categorizations stayed the same. The panel agreed a priori that cases meeting Hy's Law biochemical criteria where a role for DAC HYP was judged as 'probable', 'highly likely', or 'definite' would be designated as Hy's Law Cases, which would imply that the case was related to DAC HYP.

Cases referred to the HAC, along with their opinion are summarized below.

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Potential Hy's law cases adjudicated by HAC, summarized by FDA Medical Officer from HAC report (original submission).

ID	Rx	Days to even	Doses	Score	Type	Comment: Alternative cause or contributing factor
Study 201						
454 019	DAC 300	336	12	possible	HC	Viral Hep E suspected but IgM was negative on repeat. Remote potential relationship to escitalopram.
763 005	DAC 150	203	9	unlikely	HC	Seroconversion of HB SAg suggests acute Hepatitis B
768 011	placebo	161	6	possible	HC	Insuf. information. Perhaps viral but no serolog avail. Gilbert's accounts for elevated BR.
Study 301						
624 012	DAC 150	197	8	probably	mixed	Probably DILI confounded by carbamazepine; role of valproate and herbife was unlikely. Timing of event favors DAC over carbamazepine.
670 024	DAC 150	839	28*	unlikely	HC	Occurred off drug. Initially thought to be possible, changed to unlikely after unblinding. Consensus that Bacterial cholangitis is most likely despite lack of fever or abd pain, because enlarged lymph node & improv. after starting antibiotics.
659 019	DAC 150	264	10	unlikely	mixed	Initially possible; changed to unlikely after unblinding. Biliary disease likely; gallbladder sludge and rapid resolution go against DILI
649 006	DAC 150	729	26	Probably for	HC	Acute HC injury at 2 years is atypical for DILI but a positive dechallenge and lack of other etiologies lends to probable. Underlying Gilbert's (80% indirect). Elevated BR does not reflect liver dysfunction in this case.
517 003	DAC 150	205	4*	unlikely	HC	Prolonged latency and Slow progression to peak. MP and Rebif given as alternative MS treatment is most likely cause given close temporal relationship. Gilbert's accounts for elevated BR; MP role also possible. There is at least one published report of hepatotox attributed to MP.
604 040	DAC 150	394	14	unlikely	HC	Likely related to carbamazepine
660 007	DAC 150	650	22*	unlikely	HC	multiple antibiotics potentially hepatotoxic (augmentin and sulfasalazine) in setting of systemic illness and dx of Reiter's syndrome.
650 010	IFN	122	17	highly likely	HC	Alternative poss include spontaneous autoimmune hepatitis which is more common in the MS population or use of MP that has been associated with AIH like picture.

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ID	Rx	Days to event	Doses	Score	Type	Comment: Alternative cause or contributing factor
Uncontrolled studies						
Study 202						
909 001	DAC 300/PL/DAC 300	141 after re-start	***	Probable	HC	Drug induced Acute autoimmune hepatitis. If it had not interrupted it could have been spontaneous, but after re-starting it is likely drug induced. *** After 13 DAC/5 placebo/4 DAC
765 003	DAC 300	727	25	unlikely	HC	Pt had underlying autoimmune hepatitis to account for splenomegaly and fluctuating but persistent biochemical tests. Bouts of hyperthyroid and PTU treatment contributed to liver abnormalities.
Study 203						
553 006	DAC 150	1695	60	unlikely	HC	Orig. 2 prob and 1 poss but changed to unlikely. Normal INR. BR was elevated at baseline for unclear reasons. Hx of gallstones. Had another episode of abdominal pain and ALT/BR elevation with positive US and resolved with surgery
759 008	DAC 300/DAC 150	1376	50*	possible	HC	One hepatologist thought that it was probable because duration of ALT/AST elevation is atypical for APAPA and artichoke leaflet is actually proposed to help liver disease
453 010	DAC 150	1940	67*	unlikely	HC	Confounded by valproate. Cannot exclude that it was somehow promoted by DAC
Study 303						
649 009	Avonex/DAC150	162	4	possible	HC	Hx of autoimmune thyroiditis, rx with IFN for 2.5 yrs followed by 4 doses of DAC showed elevated transaminases with double peak pattern. Total BR increased 6 weeks after initial ALT elev. ANA 1/160; US biliary dysk and microlithiasis. Treated with IV steroids had rapid improvement of ALT and BR but there was evidence that spontaneous improvement was underway prior to steroids. This may reflect DILI, autoimmune hepatitis or drug induced autoimmune hepatitis in a pt with predisposition to autoimmune disease. IF INJURY Remains RESOLVED OFF IMMUNE SUPPRESSION a drug cause can be suspected.
622 103	DAC 150	280 (time to ALT)	5	possible	HC	Prolonged nature of the injury compatible with idiopathic autoimmune hepatitis and double peaking may in part reflect pulse steroids and CMV infection respectively although liver biopsy is not supportive (no inclusion bodies).
512 103	DAC 150	201	2	unlikely		Gilbert's, alcohol

Additional cases were reviewed by the HAC, none of which were Hy's law cases: three with non-concurrent elevations of liver enzymes and BR, consistent with Gilbert's: 301 605-002 (on DAC 150, possible, after 16 doses); 301/611-007 (on DAC 150, possible, after 23 doses); (201/761-021 (on DAC 300, unlikely, after 20 doses), and two with increased BR <2xULN (301/645-002, after 29 doses of IFNβ1a, probable, no alternative causes) and 301/609-021 (after 5 doses of IFNβ1a, unlikely, patient was pregnant).

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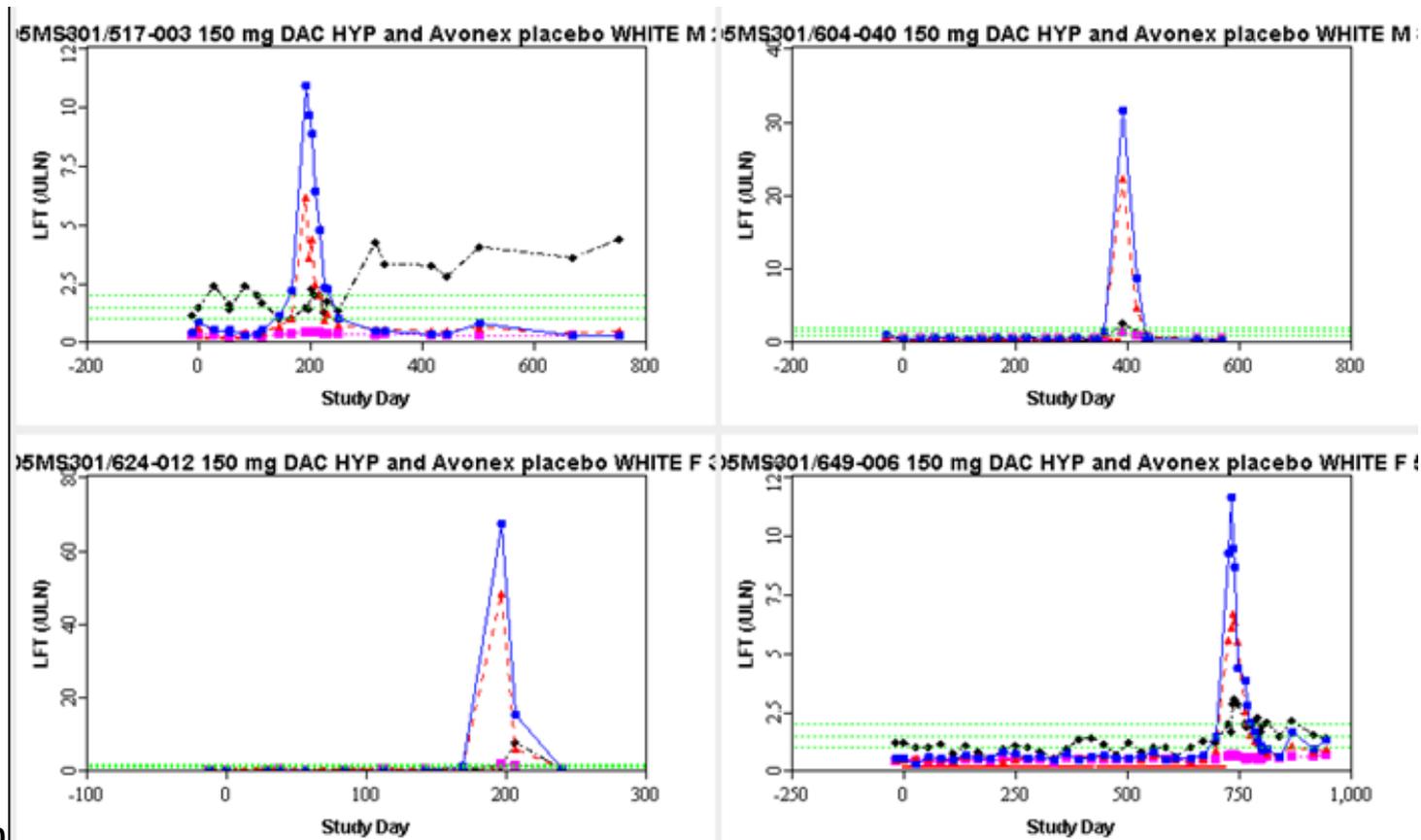
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Based on their evaluation, the HAC stated that the database did not allow concluding that DAC HYP had greater liver toxicity than INF and opined that the drug could be made available to patients with MS with monthly liver enzyme monitoring, a REMS, referral to a hepatologist and empirical use of corticosteroids in cases of suspected DAC HYP induced DILI.

I respectfully disagree with the HAC. I believe that the liver safety profile of this drug cannot just simply be addressed with labeling and a REMS. Of note, the HAC reviewed individual cases fulfilling biochemical Hy's law criteria, and aggregate laboratory data from studies 201, 301 and the Total DAC experience. The HAC did not review all cases reported as toxic hepatitis or drug induced liver injury and may have missed cases in which BR was not >2xULN (even if the ALT/AST was >10-20 x ULN). On July 24, 2015, at the FDA request, the HAC reviewed cases 201 763-004, 201 763-011, 453-026, 301 670-035, 203 506-011. For all of these subjects, the HAC opined that "DAC probably (>50%) contributed to the hepatic event reported." Upon the HAC evaluation of these additional cases, their conclusion was unchanged.

13.3.5 Hy's law cases (biochemical definition) in study 301

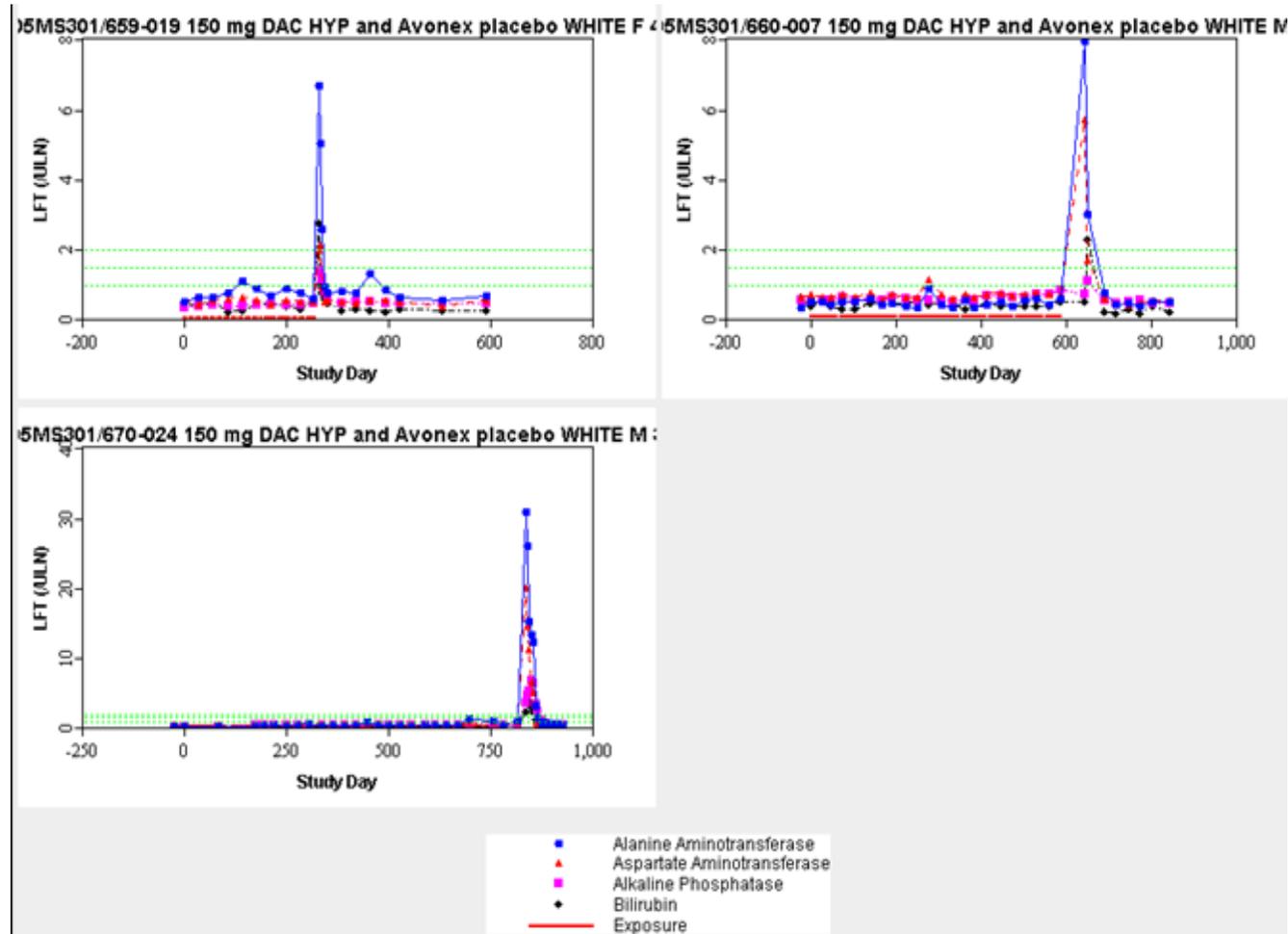
Patients with biochemical Hy's law rang ALT or AST $\geq 3 \times \text{ULN}$, BR $\geq 2 \times \text{ULN}$, ALP $< 2 \times \text{ULN}$ Empirica Study laboratory profiles provided by Dr. Ana Szarfman



Patients on DAC150

- 301/517-003: Prior Hx of Gilbert's.
- 301/604-040: Acute toxic hepatitis, confounded by carbamazepine and analgesics.
- 301/624-012: Acute hepatic failure, confounded by carbamazepine and valproate.
- 301/649-006: Hepatocellular injury, suspected Gilbert's.

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Patients with biochemical Hy's law values on DAC150 (cont)

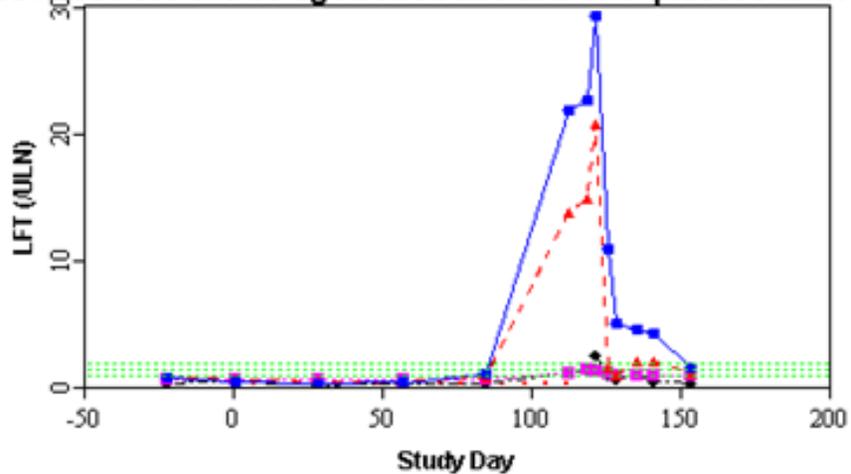


301/659-019: Biliary colic (*NOT TRUE HY's LAW CASE*)
301/660-007: Reiter's syndrome, multiple antibiotic treatments including sulfasalazine
301/670-024: Hepatic enzyme increase. Bacterial cholangitis vs. immune mediated cholangitis.

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Liver enzymes in patient 301/650-010, Hy's law case on IFNβ1a

05MS301/650-010 30 ug Avonex and DAC HYP placebo WHITE F



Subject 650-010 (IFN beta-1a)

Evaluation by Hepatic Adjudication Committee:

“25 year old woman with the serial liver chemistries noted below. Her peak serum ALT was 1002 and her peak serum total bilirubin was 55 umol/L. Serologies for Hepatitis A, B, and C, CMV and EBV were negative. Testing for AMA and ANA were negative. Anti-smooth muscle antibodies were positive at 1:20. An ultrasound of the abdomen was interpreted as “hepatitis-type diffuse changes in the liver, diffuse changes in the pancreas, and splenomegaly”. She had received pulse steroid treatment about one month before the initial elevations. In view of the positive dechallenge and absence of more likely alternative causes, the event was adjudicated as “highly likely” due to study drug, in this case Interferon beta-1a.”

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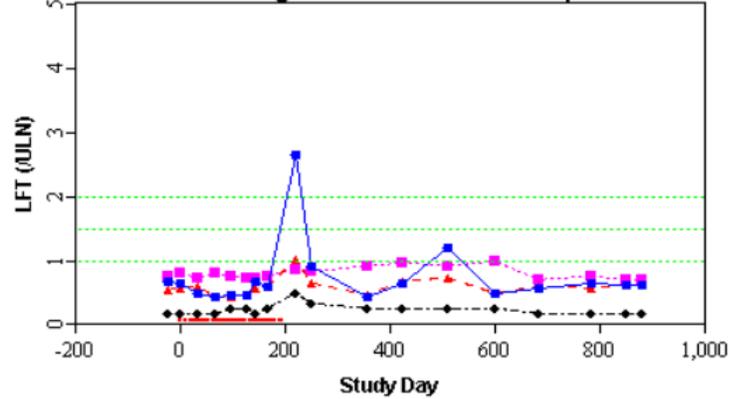
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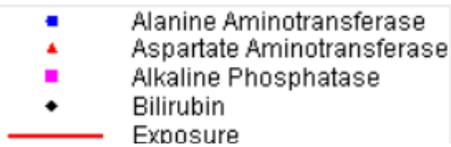
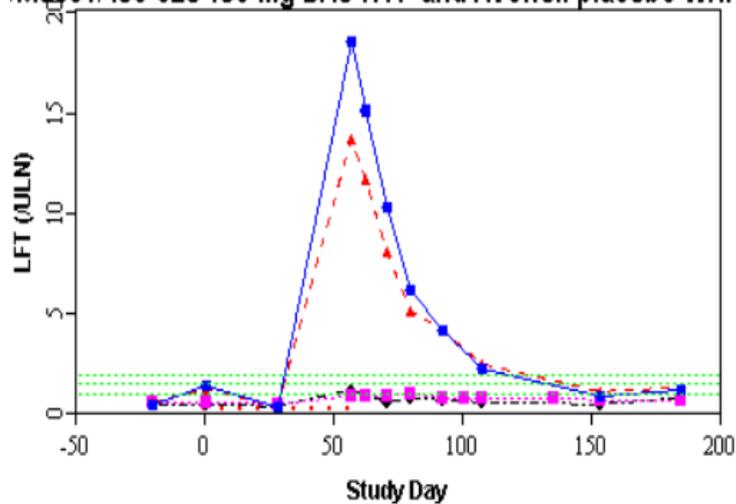
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Course of liver enzymes in patients with SAE of drug induced hepatitis in study 301 (4 on DAC150 and one on IFN)

IMS301/110-006 150 mg DAC HYP and Avonex placebo WHITE F

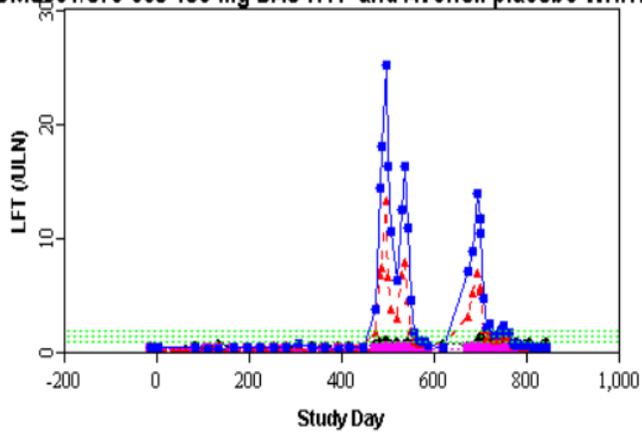


IMS301/453-026 150 mg DAC HYP and Avonex placebo WHITE F

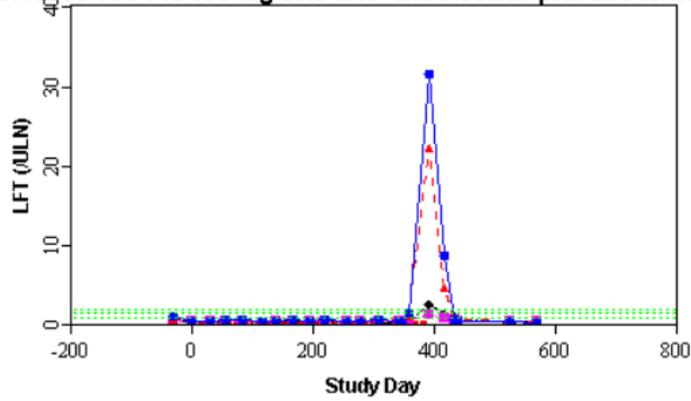


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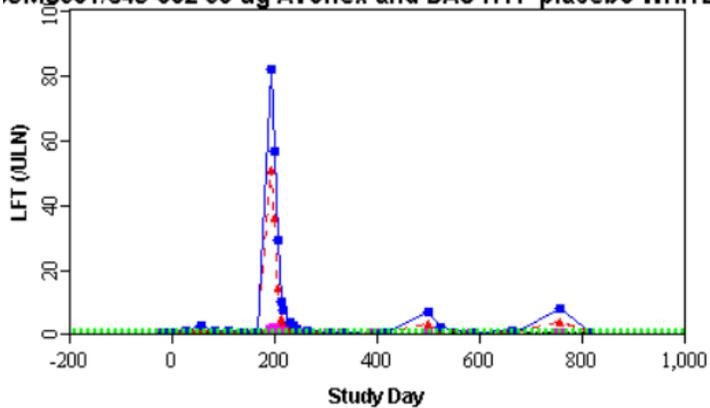
5MS301/670-035 150 mg DAC HYP and Avonex placebo WHITE M :



5MS301/604-040 150 mg DAC HYP and Avonex placebo WHITE M



5MS301/645-002 30 ug Avonex and DAC HYP placebo WHITE F



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13.3.6 FDA Liver and Immunology experts' recommendations

13.3.6.1 Hepatology consults

In August 2015, DNP requested a consultation to the FDA Liver team. To better assess the hepatotoxicity and potential need for postmarketing risk minimization, the consultants requested that the applicant provide additional information. Dr. Avigan requested extended narratives of 46 cases identified as potential DILI in the database, as well as digital pictures of cases of liver biopsy. Dr. Senior requested that AE and liver related lab datasets be submitted in a format compatible with eDISH analyses, including short narratives of cases with liver enzymes values in the Hy's law range. Datasets and narratives were submitted on October 13, 2015. ([\\CDSESUB1\evsprod\BLA761029\0042](#)). There were no digital pictures for cases that had a liver biopsy. Both consultants agree that DAC HYP is associated with serious liver toxicity. Excerpts from their reviews are included below.

- Dr. Mark Avigan's review (Reference ID# 3844895, November 9, 2015)

After providing a background on the mechanism of action of DAC HYP, Dr. Avigan notes that DAC HYP is associated with liver toxicity greater than IFN β 1a and that the decision whether to approve or not needs to be made within the context of its risk and benefits. Upon review of 46 cases he concluded that at least 3 were Probable or Probably/Possible Hy's law cases. He is concerned about the possibility of DAC HYP unmasking an underlying autoimmune diathesis involving the liver. If approved, he recommends a boxed WARNING, a MedGuide, a REMS and a postmarketing Registry for all patients who receive DAC HYP. Excerpts from his responses to specific questions posed by DNP are summarized below.

Q1. Please evaluate selected cases of DILI in this application, particularly those in which a diagnosis of AIH was made and confirm whether you think they are related to DAC HYP.

Dr Avigan's response: "In this relatively small cohort of clinical trial study subjects there was a concentration of acute liver injury events that were causally associated with the agent. In one case, fulminant liver failure and death ensued. In addition, some of the other cases were clinically severe. These cases were marked by acute elevations of serum aminotransferase levels together with increases of bilirubin, and/or INR, and/or other features of liver dysfunction or failure. Although there was variability in their time course and clinical severity, many DAC HYP-induced liver injuries occurred after long periods of continuous treatment until the onset of hepatitis. Moreover, some treatment-related liver injury events only appeared a few months after treatment discontinuation. It is notable that a number of the clinically significant cases of liver injury causally associated with DAC HYP had features of AIH. In contrast to 'classic' idiopathic AIH, many of the DAC HYP associated liver injury cases were not associated with high titers of serum ANA or other autoantibodies. However, in a few cases

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there were substantial titers of these antibodies, suggesting that the agent may also exacerbate or unmask underlying autoimmune diatheses involving the liver.”

Q.2 What approaches do you recommend for the identification and risk minimization of AIH and non-autoimmune DILI with DAC HYP based on your experience with other drugs reviewed by FDA for indications other than cancer?

Dr. Avigan’s response: “Assuming that an effective clinical and liver test monitoring program can be instituted to detect DAC HYP-induced liver injuries and manage these events appropriately, risk for serious or life-threatening outcomes in some individuals with hepatotoxicity who develop rapidly accelerating liver injury may still not be entirely mitigated. This has been a general experience with other agents associated with idiosyncratic hepatotoxicity for which regular monitoring has been recommended in product labeling. In addition, because of the long-lasting PD effects after each monthly dose, rapid spontaneous reversal of hepatotoxicity after discontinuation of the agent may not occur in every case. Thus, a careful evaluation to ensure that benefits outweigh risks for liver injury must be performed in judging approvability of this agent, as well as making treatment decisions for individual patients. Because underlying idiopathic AIH or other pre-existing autoimmune diatheses involving the liver may be exacerbated or unmasked by DAC HYP, the use of this agent in patients with these conditions should be contraindicated (or not recommended). Optimizing the detection and management of DAC HYP-induced liver injury is challenging because of the long latency between the initiation of treatment and the onset of hepatotoxicity observed in some cases. This challenge is further elevated by a need to regularly monitor patients for new onset or worsening liver abnormalities after DAC HYP treatment has been discontinued for an additional 6-12 months.” “Because some cases of DAC HYP-linked autoimmune hepatitis only resolved after treatment with high dose tapering corticosteroids with/without azathioprine, this regimen should be used to treat treatment-induced autoimmune hepatitis, when appropriate, with careful medical supervision and periodic liver test monitoring until resolution of the injury.”

Q.3 Do you believe that the risk of DILI with DAC HYP would be effectively minimized with appropriate labeling, with, or without, a REMS?

Dr. Avigan’s response: “Because of broad inter-and intra-individual variability in the clinical presentation, 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, it is unlikely that any risk mitigation strategy including periodic serum biochemical monitoring would fully eliminate risk for a life-threatening clinical adverse outcome. Thus, whether risk for DILI or other drug-related adverse events can be effectively minimized can only be determined in the context of relative benefits accrued from treatment with this agent. Nonetheless, regular assessments and monitoring at regularly scheduled appointments as could be established in a REMS are likely to reduce serious outcomes, if both patients and HCPs adhere to this practice

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and diagnostic interventions and appropriate treatment alterations are made in a timely manner if liver injury or other adverse events are detected.”

Q.4. What other additional studies/analyses would you recommend that the applicant conduct prior to or after approval to better characterize the hepatotoxic profile of DAC HYP?

Dr. Avigan’s response: Identification of the long-term treatment effects on safety and efficacy of DAC HYP for MS “could be accomplished by formation of a patient registry in which all treated patients would be enrolled and tracked during and after the end of treatment with the monoclonal antibody.” “Because T-cells with opposing functions that promote either autoimmunity or tolerance are targets for anti-CD25 treatment, it is critical to predict instances or conditions when unintended autoimmune organ injuries will occur during treatment with DAC HYP. To strengthen the review of DAC HYP in conjunction with other similar products being considered for approval, expert input from a cellular immunologist with expertise in experimental treatment models that affect autoimmunity and tolerance should be sought.”

- Dr. John Senior’s review (Reference ID: 3874751, January 18, 2016)

Dr. Senior provided a detailed review of the fatal case of autoimmune hepatitis and commented on Dr. Avigan’s review of cases. His conclusion is summarized below:

Dr. Senior does not think that an effective monitoring program can be put into place because of “several realities.” “It is wishful thinking to accept that labeling, even boxed warnings, will be read, understood, accepted, and followed by all the treating neurologists.” The dead patient 909-001 “faithfully came to clinic every 4th Tuesday morning” for almost two years. That did not protect her from a fatal outcome. “Educational programs compete with advertising and promotional efforts by marketing personnel.” “FDA has no authority to require complete reporting of what happens to all patients to whom a new and dangerous drug is prescribed.” “Voluntary reporting doesn’t work, not matter how well intended it may be.” He also states that in the case 909-001 “DAC HYP seems to have generated a clone of lymphocytes that attacked her liver cells” and even after its serious adverse effects were detected and DAC HYP was stopped “the attack continued until virtually all her hepatocytes were destroyed and she suffered what appeared to be an immunological hepatectomy and died 90 days after the last dose on DAC HYP.” He concludes: “I am not impressed that DAC HYP 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. It is evident that simply detecting it earlier by monitoring or REMS, if reported, would not help patients unless neurologists knew what to do about the findings. It is not known if earlier treatment with steroids would abort the progression of autoimmune-like destruction of hepatocytes and give the injured liver a chance to heal itself by regeneration. 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 DAC HYP. My

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recommendation is Complete Response, and careful reevaluation of the data to see what more can be learned from the extensive studies that have been done, and are still continuing.”

13.3.6.2 Immunology consult. Dr. Amy Rosenberg’s review (Dated May 4, 2016).

Dr. Rosenberg pointed out to the abundant literature on the relationship between CD25, IL2RA, FOXP3 and Treg downregulation/dysregulation and the development of autoimmunity and lymphoproliferation. (1)(2)(3)(42)(43)

I quote Dr. Rosenberg’s recommendations.

“Approvability of the application has to be considered in the context of overall risk and benefit. Given the spectrum of SAEs pertaining to autoimmunity induced by DAC, the lack of ability to predict patients at risk, the lack of an appropriate monitoring strategy, the uncertainty whether even early detection and treatment of such SAEs would prevent worsened disability and death (eg the cases of new brain stem lesions in 2 patients who died on treatment), I recommend that this application either not be approved until the sponsor can address these issues and identify a strategy for patient selection, early detection and mitigation or be restricted to a subset of patients where the risk/benefit ratio is considered favorable. Ultimate approval should be contingent upon the sponsor’s development of assays that are capable of predicting and rapidly detecting autoimmune AEs as well as elaboration of better monitoring and treatment strategies for patients who develop autoimmune AE.”

Dr. Rosenberg strongly recommended a Center Director Briefing and has proposed an extensive list of studies that the applicant should consider. I quote her recommendation regarding additional studies.

“The sponsor has not identified biomarkers or genetic/proteomic signatures that predict autoimmunity but this should be much more aggressively explored. We suggest that the sponsor pursue the following:

- Correlate the extent of Treg depletion coupled with CD56hiNK enhancement in patients with autoimmune mediated AEs vs those not manifesting such responses and assess whether this could be used as a basis to develop an assay to predict autoimmune AEs
- Develop an in vitro assay of lymphocyte proliferation (spontaneous and induced) which could potentially provide a biomarker of autoimmunity. Given the lymphoproliferation associated with loss of Treg function, this should be evaluated by the sponsor in patients who developed autoimmune AEs vs those that did not.

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- Develop an RNA-seq analysis of lymphocytes to assess for a signature of autoimmunity that could be utilized to identify informative biomarkers.
- Assess *function* of Tregs following recovery of significant levels on cessation of DAC
- Assess earlier biomarkers of liver injury
- Investigate the presence of autoantibodies to the spectrum of autoantigens observed in patients with mutations in IL-2RA and CTLA4 and their correlation to symptomatic autoimmune disease
- Consider approaches to mitigating severe autoimmunity that consider the likely mechanism of action, Treg depletion. Given the 6 month time to recovery of such cells following cessation of DAC, strategies that would increase Treg numbers or functionality, together with other immunosuppressive agents may more rapidly reverse and prevent tissue damage. “

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13.3.7 BLOOD AND LYMPHATIC TISSUE DISORDERS SOC, SAE AND AE DROPOUTS

Listing of selected SAE

ID	PT	Comment
201/ 454-005	LYMPHADENO PATHY	31 F. Lymphadenopathy along with peritonsillar abscess, on Day 59, probably reactive to infection. Treatment interrupted (one dose [3 rd]). Resolved with antibiotic treatment after 11 days. (later ALT<3 uln and BR<2 wk 24-44)
301 660-007	AGRANULO CYTOSIS	29 M. Agranulocytosis on Day 596, soon after being diagnosed with Reiter's syndrome treated with trimethoprim sulfamethoxazole and sulfasalazine. He developed Reiter's Syndrome on day 582, after 22 doses of DAC HYP 150. Patient also had pityriasis rosea, seborrheic dermatitis (on Day 304, not resolved) and agranulocytosis, leading to drug withdrawal. This case of reactive arthritis, seborrheic dermatitis and agranulocytosis is confounded by use of sulfa drug. Agranulocytosis resolved after 58 days. <i>As of a 10/10/15 response, the event of Reiter's syndrome has not resolved.</i>
301/ 453-049	IRON DEFICIENCY ANAEMIA	35 F presented MS relapse on Day 464; reported non-serious moderate anemia on Day 504, and mild, serious iron deficiency anemia on Day 603 that resolved approximately 2 months later after iron treatment. No action was taken with drug; the last dose was on Day 646.
301/ 437-001	ANAEMIA, LYMPHADENO PATHY	46 F, had mild anemia from the beginning of the trial and reported a SAE of anemia on Day 85, which resolved on Day 96. Non-serious AEs reported in this patient were MS relapse, impaired healing (local extravasation) and intermittent pruritus. On Day 225 she developed mild arthralgia from Day 224 to 644. She also had "infusion related reaction" from Day 222 to 365. Concomitant meds at the time of the event were iron, fluoxetine, lamaline and methylprednisolone. She had been taking fluoxetine before she started DAC. On Day 531 a non-serious but "severe" AE of generalized lymphadenopathy and drug was withdrawn; the event was reported as serious on Day 553 and resolved on Day 743. Ultrasound of the lymph node areas showed "posterior cervical and right subclavicular, multiple, enlarged lymph nodes consisting of frankly hypoechogenic elements of about 1 cm in size and of inflammatory type." Tomodensitometry showed many bilateral, basal, pulmonary, parenchymatous micronodules, with some of them calcified and atypical, but of a somewhat sequellar appearance; unusual calcifications of the tracheobronchial cartilaginous

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		rings; hypodense hepatic lesions suggesting simple cysts” On (b) (6), a lymph node aspiration showed polyadenopathy syndrome. On (b) (6) positron emission tomography/computed tomography (PET/CT) scan showed marked hypermetabolism of supradiaphragmatic and subdiaphragmatic lymph nodes measuring 1 cm and <1 cm, respectively. Excision bx of spinal lymph node showed benign lymphoid hyperplasia. Laboratory showed low Hb throughout the study with no evidence of abnormal WBC or lymphocyte count. Drug was discontinued; last dose was in (b) (6) Lymphadenopathy was considered resolved in (b) (6) although lymph nodes were still visible with ultrasound (b) (6).
301/ 477-005	LYMPHADENITIS	47 year old F developed moderate lymphadenitis on Day 839. She had small lymphadenopathies (up to 17 mm diameter) in several areas. Diagnosed with “polyadenopathy syndrome”. PET scan showed hypermetabolism in the bilateral axillary, right cervical, paratracheal, hepatic hilar inguinal and external iliac chains. LN biopsy showed non-specific reactive follicular lymphadenitis.” Resolved after 86 days. Drug was discontinued (Last dose on Day 815) and event treated with MP.
301/ 480-002	LYMPHADENOPATHY LYMPHOPENIA THROMBOCYTOPENIA	34 F developed SAEs on Day 338, Approx. one month after the last dose of DAC 150 (which was on Day 305), leading to drug withdrawal. Events lasted one week. Non-serious events prior to these were trigeminal neuritis since Day 326 and back pain on Day 334, which were treated with carbamazepine and diclofenac, respectively. She was also treated with tizanidine. <i>The use of carbamazepine and diclofenac could explain such hematologic reaction.</i>
301/ 610-009	LYMPHADENOPATHY	42 F, presented non-serious erythema on day 20. She was diagnosed with Lyme disease on day 33 which was reported resolved on Day 576. During this time she also presented non-serious microcytic anemia and arrhythmia (extrasystoles). Lymphadenopathy, pyrexia and EBV infection were diagnosed on Day 455 with transient mild ALT/AST increased on Day 475. EBV infection reported as resolved on Day 559; lymphadenopathy again reported Day 572 to 576, along with a skin lesion. A “benign neoplasm” was reported on Day 506 to 556. Concomitant meds included paracetamol for the first year. Labs showed one time eosinophil increased on day 335. Labs showed increased platelets throughout the trial and intermittent occult blood. Atypical lymphs identified on Day 464 and 552.
301/ 614-037	LYMPHADENOPATHY	50 F. After second dose had headache, malaise, nausea, pyrexia, asthenia, musculoskel stiffness, hypoesthesia, paresthesia. Since Day 320: pain in extremity, seborrheic dermatitis and mild

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		lymphadenopathy. Prior to Day 320 she was taking fexofenadine. On Day 403 developed eczema of the face reported as resolved on Day 451. Non serious AE of enlarged lymph node reported on (b) (6). He had a fine needle aspiration bx as well as CMV and EBV tests which results were not reported. On (b) (6) (Day 530), after 19 doses of DAC, a SAE of lymphadenopathy was reported because he had surgical biopsy. Bx showed "inactive, tumor-free node" and even was considered resolved. DAC HYP was resumed. LABS were reportedly normal.
301/ 670-017	THROMBOCY TOPENIA	25 M. Last dose on Day 787. On day 815 presented thrombocytopenia, on Day 845 had rash. No conc. meds prior to thrombocytopenia and rash. No action taken with drug because was the end of trial. <i>As per concom meds dataset he started prednisone 60 mg on 4/12/14 (Day 867) and down to 40 mg/day on Day 892 but needed to increase it again. Eventually able to come down to 20 mg/day on Day 940 (6/24/14) and treatment was ongoing as of the SUR (cut-off February 2015. As per 10/10/15 response, event resolved on 11/9/2014. So it took 7 months to resolve.</i>
301/ 743-001	LYMPHOID TISSUE HYPERPLASIA	41 F, On Day 785 presented non-serious lymphadenopathy, then, SAE lymphoid tissue hyperplasia (moderate) on Day 812 for 4 days. Not taking concomitant meds at the time. Tuberculosis was diagnosed on Day 943, treated with quadruple therapy. Last dose was on Day 928. Listed as "No action taken with drug" but drug was in fact withdrawn (last dose on Day 925).
202/765- 003	LEUKOPENIA	25 F. Presented Moderate leukopenia on Day 771 of DAC 300. Resolved on Day 868. No action taken with drug because drug already withdrawn. Same patient who developed urticaria, autoimmune thyroiditis and chronic autoimmune hepatitis.
203/303- 005	HISTIOCYTOSIS HAEMATO PHAGIC	37 M. Severe event of Hystiocytosis hematophagic on Day 1206 of DAC HYP treatment. Received DAC 300 in 201 and 202, and DAC 150 in study 203. Resolved on Day 1234. Overall picture of a florid reactive immune state possibly triggered by an infection by an unidentified pathogen. This case was later diagnosed as catastrophic antiphospholipid antibody syndrome in patient with suspected septicemia . He presented inflammatory arthritis with +Rheumatoid Factor, followed by increased liver enzymes and viral skin infection with infarct of the fingertips and renal impairment. "No action taken with drug" because drug had already been stopped. See narrative under SAE of Infections.
203/ 501-014	LYMPHADE NITIS	31 F. Presented Moderate lymphadenitis on Day 818-819 of study 203. Received DAC HYP 150 in 201, placebo and DAC 150 in 202 and DAC 150 in 203. Drug interrupted.
203/506- 003	IRON DEF. ANAEMIA	45 F. Moderate iron deficiency anemia on Day 459-534. Received Placebo in 201, DAC HYP 300 in 202 and DAC HYP 150 in 203. No action taken with drug.
203/ 508-009	LYMPHADENO PATHY	29 M, Mild lymphadenopathy on Day 1517 to 1652. Received DAC HYP 300 in 201/202 and 150 in 203. No action taken with drug.

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203/ 553-001	LYMPHADENO PATHY	50 F. Moderate lymphadenopathy on Day 1090-1107 of DAC treatment. Received DAC 300 in 201/202 and DAC 150 in study 203. Drug interrupted.
203/ 767-002*	LYMPHADE NITIS	27 M. Moderate lymphadenitis (bubo adenitis neck and inguinal node) on day 1103-1111. Received Placebo in 201 and DAC 150 in 202/203. Pt had non serious AE of lymphadenitis, bronchitis and chronic prostatitis during the study. The patient had a +RF and was ADA and NAb positive in 201. Hospitalized post SUR cutoff with neck side and inguinal lymphadenitis. Excisional bx of cervical node showed signs of follicular hyperplasia. Oncologist assessed LN as "within normal range". Resolved after 9 days. No action taken with drug.
203/ 761-004*	Lymphoma	44 M. 15-day report. See narrative under SAE in Neoplasms SOC.
203/100- 002 *	Hemolytic anemia, hematuria	44 F. 15-day report. Completed 202. On August 14 2015 (3 ½ years of rx) had fever, chills and burning micturition, dx as UTI treated with cephalosporin. On (b) (6) admitted to hospital due to fall in Hb (3.4g/dl, normal range 12 to 15), and low WBC (2.5, normal 3.8 to 4.8, no units provided). Liver and renal labs were normal. She had microscopic hematuria. Treatment included pantoprazole, cefoperazone and sulbactam. On trying to cross match the blood "there was some antibody in the blood which was interfering with cross matching". Patient discharged (b) (6), with Hb of 10.4 g/dl; event "resolved with sequela." <i>Case confounded by antibiotic use. Role of DAC cannot be excluded. As per fu received 9/25/15, she had positive Direct and Indirect Coombs test, with 6% reticulocytes (normal 0.2-2%). She was given 3 units of PRBC and was treated with corticosteroids (prednisone 20 mg bid) (b) (6) As of September 21, 2015, her CBC was normal. No DAC antibody testing.</i>
203/ 205-004*	LYMPHADENO PATHY ("inflammatory adenopathies") (CMV INFECTION?)	46 F. "Inflammatory adenopathy." Resolved. Drug apparently re-started without recurrence. Event occurred March 2015. Last dose prior to event Feb 26, 2015. Total number of doses was 50. Fever x 2 weeks; 5 cm adenopathies left axilla with fever and hepatosplenomegaly. Admitted overnight for further testing. Event considered resolved (b) (6) Med restarted April 27, 2015. Conc med included pregabalin and atenolol since July 2014. Histopath report from left axillary adenopathy biopsy done (b) (6) showed morphologic changes associated with a benign proliferative process , which was hyperplastic and of viral origin. At the subcapsular level histiocytes were identified with haematophagocytic activity and maturing lymphs at the center. There were no signs of malignant transformation. Viral testing was initially negative. The event was considered related to study medication. On follow up (IND report 2015BI042350 9/24/15), the event resolved and that there was no hepatosplenomegaly at the time of lymphadenitis. The patient remains

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		asymptomatic. Only one dose of DAC HYP had been missed. "The investigator further confirmed the diagnosis of CMV infection. " (<i>despite CMV IgM negative antibody testing</i>)
203/ 453-003*	LYMPHADENO PATHY. NHL	59 F. 15-day report. 7 years since starting in study 201. T cell lymphoma. See narrative under SAE of Neoplasms.
203/ 458-017*	LYMPHADENO PATHY	On (b) (6) after unknown number of doses patient hospitalized for 2 days for extirpation of left axillar lymph node. Subject had bilateral axillar and neck lymphadenopathies (2 to 2.5 cm). Bx showed non-specific reactive changes with no evidence of malignancy. The event was considered resolved (b) (6). Subsequently, a lymph node appeared before the right earlobe, "likely benign." Patient was scheduled to have follow up in July 2015. <i>An IND safety report for this case (2015bi151747) erroneously identified as initial 15-day report says that the event of lymphadenopathy resolved (b) (6) and does not mention the new lymph node near the earlobe.</i>
303/ 439-007	PERNICIOUS ANAEMIA	36 F. See narrative under GI disorders SOC (chronic atrophic autoimmune gastritis)
303/ 453-002	LYMPHADENO PATHY	34 M. Severe LN on Day 1373 of DAC treatment. Drug WD after 48 doses of DAC 150. Swelling of axillary region. No pain. CT chest: bilateral cervical, supraclavicular and axillary lymphadenopathy, also enlarged lymph nodes in chest and abdomen. Bx was reportedly negative but it is not available. EBV testing was negative. Dx of lymphoma was suspected but not confirmed. Event was ongoing at time of the SUR. As per 10/10/15 response to request for information the event "resolved"
303/ 457-006	LYMPHOPENIA	32 M. Received IFNβ1a in 301. Severe lymphopenia on Day 28-31 of study 303. Drug interrupted.
303/ 571-008	LYMPHADENI TIS and PNEUMONIA	30 F. Cervical and axial lymphadenitis ("mild") on Day 772 to 813. After 28 doses. No action taken with drug. Subject still in study. Axial LN was concurrent with pneumonia along with fever and slight aching. No bx done. Treated with cefuroxime, Cipro and dexamethasone. Event resolved after 42 days.
303/ 604-027	LYMPHADENO PATHY	35 F. Mild LN. Drug interrupted. Occurred in March 2014 (Day 981 on DAC), after 34 doses of DAC. Palpable tumor in the L submandibular area that was suspected to be an enlarged lymph node but it was a salivary gland with chronic inflammation and focal fibrosis . Rx with MP. Drug was interrupted but then continued. Not resolved at time of SUR. On follow up, the event of lymphadenopathy was considered resolved on August 2015. (<i>In my opinion this could be Sjogren's syndrome</i>)
303/ 613-009*	LYMPHADENO PATHY	47 F. Mild LN, on Day 1075 of DAC treatment. Drug interrupted after 39 doses of DAC. Node in supraclavicular region. US showed supraclav and axillar lymphadenopathy. Excisional biopsy showed "follicular reaction". Reported as "No action taken" with drug. As of 10/10/15, event is ongoing.

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303/ 629-008*	LYMPHADE NITIS	51 M. Severe event on Days 1123-1172 of DAC treatment. Drug WD. 41 doses of DAC 150. Drug WD. FINA cytology suggested low grade malignant lymphoma but on further analyses was thought to be reactive follicular hyperplasia . Resolved after 50 days. There were T and B cells, T cells in the interfollicular sites were CD5+. Lymphoid follicles showed +bcl-2 marker.
303/ 649-009*	THROMBOCYTO PENIA	Moderate. Pt had received IFNβ1a in 301. Thrombocytopenia occurred on Day 251 of 303. No action taken because already off drug. Event occurred after event of autoimmune hepatitis and improved with corticosteroid treatment. <i>As per most recent follow up the patient was able to be tapered off steroids without further hepatitis or thrombocytopenia.</i>
303/ 601-004*	LYMPHADENO PATHY	26 F. Unknown number of doses. CT of Chest & abdomen showed enlarged axillary, supraclavicular and inguinal nodes. Histology: Reactive proliferation of B zone . Drug interrupted and later discontinued on Jan 23, 2015. Event not resolved.
303/ 617-003*	Thrombocyto penia (also anemia and lymphadeno pathy)	2015BI088120. Hx of bladder neoplasm. On (b) (6), admitted to hospital due to general weakness, worsened neurological status, and worsened skin lesions which she had for several days preceding the hospitalization. A viral infection was suspected. Treatment for itching was started. During hospitalization, erythematous lesions were found with superficial erosions and was treated with topical treatment. Hemoglobin (HGB) was 8.30 mmol/L , (reference range 8.4-11.0), hematocrit (HCT) 0.38 (reference range 0.42-0.55), platelets (PLT) 110 G/L (reference range 140-440). On (b) (6) numerous hypoechoic tissue consistent with lymph nodes were identified in the abdominal cavity, pelvis and R axillary fossa . CRP was 11.6 mg/L (reference range <5.0), HGB 7.90 mmol/L, HCT 0.371 L/L and PLT 80 G/L. On (b) (6) Hepatitis B, C and HIV testing was negative. Treatment included methylprednisolone 40mg daily, omeprazole, potassium, hydroxyzine, clemastine and drotaverine. (b) (6) There were non-specific nodules in the adipose capsules of both kidneys (suspected melanoma metastases). The visceral lymph nodes were not enlarged and the retroperitoneal lymph nodes were <10 mm. There was suspicion of tumor in the area of the bladder. A PET Scan was expected. Needs FU.
303/ 617-005*	LYMPHADENO PATHY	27 F. Unknown number of doses. US: identified numerous abnormal lymph nodes in R axillary fossa. Hypoechoic up to 15 mm in size along the long axis, seemed to be of a reactive nature. CT chest showed clusters of axillary lymph nodes enlarged up to 20 mm, including LN under pectoralis major muscle. No mediastinal LN. Normal lung parenchyma and mediastinum. DAC was WD (b) (6) and ultrasound was to be repeated after one month. No treatment was given for lymphadenopathy. Drug discontinued. Not resolved, still ongoing at time of last follow up.

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303/ 657-017*	LYMPHADENO PATHY	26 M. Adenopathy L axilla after 34 doses of DAC. First noted May 2014. No action taken. Underwent excision (b) (6) Small lymphocytes, disperse histiocytes, isolated plasmocytes and eosinophilic granulocytes in the paracortex were noted. Immunohistochemical findings revealed CD20 positive in follicular B lymphocytes, which appeared less frequently parafollicularly (3+). Bcl-2 positive in B cells of lymphatic nodules and T lymphocytes, negative in GC (2-3+), CD3 positive in T lymphocytes of paracortex and interfollicularly, CD68 (PGM) positive in disperse centrofollicular and parafollicular histiocytes, S100 protein positive in interdigital dendritic cells, and CD1a negative Read as reactive follicular hyperplasia . No evidence of clonality. Resolved.
303/ 405-002*	LYMPHADENO PAHTY	49 M. Received IFNβ1a in 301. LN of mandibular region after 13 doses of DAC. Lymphadenectomy performed. Follicular hyperplasia. No malignancy. Resolved. No action taken with drug.
302/ 162-106	LYMPHADENO PATHY	46 F. Drug WD after 22 doses of DAC HYP 150. Event reported on Day 735 of study 302. Longstanding bilat posterior neck LN that got worse and did not respond to antibiotic or corticosteroid treatment; also axillary, neck and groin LN. FINA of R cervical LN (b) (6) showed no definite immunophenotypic evidence of NH B cell lymphoma. Path showed minute fragments of reactive lymphoid tissue. An excisional bx of L LN was read as benign reactive lymph node. In (b) (6) she reported cough and weight loss; CT scan of chest showed axillary nodes, no mediastinal LN mentioned. Drug suspended and LNs improved. When study drug was reintroduced in June 2014, LN recurred and drug was WD. The event of “diffuse lymphadenopathy” improved slowly. As per fu IND safety report, it was considered resolved with sequelae on September 2015, more than one year after last dose of DAC.
302/ 463-103*	Hemolytic anemia	42 F. The patient was seen in ER (b) (6) because of conjunctival jaundice after 35 doses of DAC HYP . No prior medical history or concomitant medications. She felt dizzy and had a syncopal episode. At hospital Hb 74 g/l (120-160). HTC 021 (0.35-0.46), MCV 122 (80-96), lymphocytes 0.09 (0.2 – 0.4). Total BR 5.5 mg/dl (0.2-1.6) (Total BR in umol/L was 88.1 [2-17]), glucose 6.1 (3.3-5.6); Direct BR 10 (2-5.1) CRP 12.4 (0.3-5). Abdominal US showed status post cholecystectomy, enlargement of liver and spleen and liver steatosis. Positive Coombs test. A consultant hematologist diagnosed massive intravascular hemolysis, probably due to secondary autoimmune hemolytic anemia (AIHA). Because no response to steroid therapy she was transferred to the intensive care unit (ICU) at another hospital (b) (6) DAC HYP was discontinued. The treatment included MP 250 mg/day for 3 days and 500 mg/day for 2 days, fluids, allopurinol, folic acid, heparin, fluconazole and insulin. Hb gradually increased, MP was

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		reduced and switched to prednisone 1 mg/k/day. “The discharged diagnosis included autoimmune hemolytic anemia (warm), positive PAT, NAT and ENZ. As per fu information submitted 9/25/15, she received corticosteroids (b) (6) and is currently off steroids. As of (b) (6) her hemoglobin was normal. She was DAC antibody negative throughout the study up to Week 96. <i>In my opinion, immune mediated hemolytic anemia may be related to DAC.</i>
302/ 502- 108*	NEUTROPE NIA	Reported as IND safety report on AUGUST 2015. Most recent dose on Jul 31, 2015. Unknown number of doses. Hospitalized with fever. Diagnosis included neutropenia medicamentosa and MS. Event of febrile neutropenia improved after treatment with wide spectrum antibiotics and antifungals. No further episodes occurred after drug discontinuation. It appears related to study drug.

Table includes follow up information submitted on July 28, 2015 at the FDA request. In addition to cases reported as part of the original application and the SUR, the listing includes patients reported after the cut-off for analysis of the SUR or as an IND 15-day safety report (marked with *) which were not included in the Total DAC HYP analyses, for which there is incomplete information (including 2 cases of hemolytic anemia and 14 additional SAE of lymphadenitis/ lymphadenopathy). Note that several cases were not resolved at the time of last follow up. *Reported after SUR data cut-off as part of response to FDA request for information or Submitted as 15-day safety report (Not in ISS analyses.)

A case of hemolytic anemia occurred in a patient receiving DAC HYP after initiation of alternative MS therapy (IFN beta 1a), diagnosed 184 days after last dose of DAC, but symptoms started before 180 days, as follows.

301 472-005, 50 F, SAE of Coombs positive hemolytic anemia reported (b) (6) after 36 doses of DAC HYP 150, on day 1165 of treatment. As per the narrative, impaired liver function and cholestasis were noted in the subject’s history “for some years ago.” Mild ALP elevation and increased GGT up to 3xULN were noted since September 2011. ALT/AST/BR were normal. Throughout the study, HTC was 34-37% and Hb was 110-120 g/L. Last dose of DAC HYP was December 18, 2013. Alternative MS therapy with IFN was started on April 9, 2014. Anemia “non-serious” (with HTC 24% and Hb of 80 g/L) was noted during a site fu visit on May 7, 2014. On (b) (6) she went to the ER with jaundice. Hb was 72 g/L, MCV 100, HTC 22%, platelet and WBC were normal. ALT, BR, PT and PTT are provided but without reference ranges. Coombs test was positive (1/300) and reticulocytes were 9%. On (b) (6) days after last dose of DAC HYP she was hospitalized with diagnosis of hemolytic anemia. “Widespread bone marrow hypermetabolism was observed, probably as a reaction to the anemia. Bilateral adrenal adenomas were probable.” IFN was stopped. She was treated with prednisone 60 mg twice daily (b) (6) followed by prednisone tapering. As of Nov 2014 when was still on prednisone 10 mg/day, and as of October 2015 the event was still not resolved. *Immune hemolytic anemia may be related to both DAC HYP and interferon. Severe anemia was observed at least 1 ½ months earlier than the reported AE.*

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Listing of selected patients who discontinued due to non-serious AEs in Blood and lymphatic system disorders SOC as of the SUR.

IUSUBJID	AE PT	Comment
303/ 105-003	LYMPHADENO PATHY	43 F. Onset Day 150, after 6 doses of DAC 159; Hx of hypothyroidism, irritable bowel syndrome, type 2 diabetes and asthma. Concom. Meds included bupropion, ibuprofen, gabapentin, paracetamol, salbutamol, tizanidine, tramadol. Not resolved at time of SUR but eventually resolved. Narrative does not provide details as to the location or size of the lymph nodes.
301/ 441-010	LYMPHOPENIA	54 M. Onset Day 590 after 22 doses of DAC. Concom med was paracetamol. He developed lymphopenia at 24 weeks, with total lymphocyte counts ranging from 0.5 to 0.9 x 10 ⁹ /L, on Days 168-421). On day 505, low lymphocyte count was reported as an adverse event. Other hematologic values were normal. Drug was interrupted; the event was considered resolved on Day 527. DAC HYP was resumed on Day 533. Event of lymphopenia <u>recurred, upon rechallenge</u> (Lymphocyte count 0.7 x 10 ⁹ /L). Drug was discontinued. Lymphopenia resolved after 2 months.
301/ 605-002	LYMPHOPENIA	35 F hx of hyper BR. Concom meds ibuprofen, naproxen baclofen topical steroids. At screening TBIL 22 umol/L, nl ALT (normal up to 21). Withdrawn for lymphopenia on Week 60, Day 421 (lymphocyte count 0.65 x 10 ⁹ /L; normal 0.9 to 4.28). On Day 421 patient also had mild ALT/AST/ALP and TB elevation. On Day 450, approx. 29 days after discontinuation, liver enzymes peaked ALT 102 U/L (nl up to 34), AST 105 U/L (nl up to 34), ALP 187 U/L (nl up to 106) and Total BR was 28. Event of lymphopenia and liver enzyme elevation resolved on Day 478 without treatment. Prior to event of lymphopenia patient also had AE of hyperthyroidism and microcytic anemia. As per the HAC, Gilbert's may have contributed to elevated BR.
301/ 610-009	LYMPHADENO PATHY	Onset Day 512. Included thoracic lymphadenopathy. As per fu on September 30, 2015, event is still ongoing.
203/ 563-002	LYMPHADENO PATHY	Onset Day 1725, not resolved. As per follow up information submitted on September 30, 2015, event is ongoing and it is being observed further to exclude lymphoma.
302/ 454-102	LYMPHADENO PATHY	Onset Day 703, not resolved at time of SUR, but eventually resolved. As per JReview PP patient also had dyspnea and psoriasis along with lymphadenopathy.
303/ 609-013	LYMPHADENO PATHY	Onset Day 1121, end 1212. Had multiple events; included serious rash and hilar lymphadenopathy suspected of DRESS, in my opinion consistent with sarcoidosis.
303/ 727-002	LYMPHADENO PATHY	Onset Day 1098, not resolved as of last follow up.

Source: ADAE3 SUR datasets. Includes outcome as per follow up submitted on September 30, 2015.

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13.3.8 CARDIAC SOC, SAE AND AE DROPOUTS

SAE in Cardiac SOC

201/ 500-003	45 F	Mild M Ischemia on day 320 after 31 doses of DAC 300. No action taken with drug. Resolved after 2 days.
203/ 510-005	44 M	Mod MI on Day 1683, after 62 doses of DAC 150. No action taken with drug. Resolved after 5 days.
301/ 129-001	50 F	Mod Bradycardia on Day 710 after 26 doses of DAC 150. Drug interrupted. Resolved after 3 days.
301/ 606-023	51 F	Mod palpitations on Day 587, after 41 doses of DAC 150. No action taken with drug.
303/ 554-007	42 F	Cardiomyopathy categorized as mild on Day 160 of study 303. This patient received IFNβ1a in study 301 and DAC 150 in study 303. She also developed a SAE of elevated liver enzymes in 303 and is described in detail in the Hepatobiliary disorders SAEs. The cardiomyopathy appears to be caused by hypertensive heart disease. No action taken with drug. Resolved after 6 days.
301/ 744-007	46 F	Cardiorespiratory arrest on Day 202 of study 301, after receiving 4 doses of DAC 150. Fatal aspiration pneumonia and sepsis subsequent to acute exacerbation of MS. Discussed under Deaths.
303/ 433-003*	58 M	(IND safety report) 58 year-old male subject with history of hypertriglyceridemia and recent vaccination against flu, diphtheria, tetanus and meningitis, was hospitalized (b) (6) for “cardiac decompensation” and bilateral pleural effusion 18 months after initiation of Daclizumab HYP therapy in the extension study (he received 27 doses of DAC 150 in study 301 and 19 additional doses in study 303). Concomitant medication included gabapentin, metformin, ibuprofen and paracetamol. The patients had symptoms of chest pain and increasing dyspnea for the previous 6 months. In (b) (6) a cardiac ultrasound showed dilated cardiomyopathy , ejection fraction of 41% and pericardial effusion. He underwent thoracentesis and pleural biopsy (cytology and bacteriology pending). The study drug was temporarily discontinued. In (b) (6) the PT was changed to “heart failure.” Possible etiologic factors include myocarditis (because of recent vaccination) or <u>daclizumab related event</u> . At a follow up cardiology visit (b) (6) an EKG showed sequelae of myocardial infarction in the anteroseptal leads and left posterior hemiblock. An echocardiogram showed an EF of 30%. The cardiologist noted that the patient had

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		<p>hyperlipidemia but no other risk factors for CAD but suspected that the patient had a MI back in (b) (6), leading to congestive heart failure and pulmonary edema. The patient underwent coronary angiogram with stenting of the circumflex and LAD coronary arteries. Drug was discontinued. The investigator considered the event <u>related to study drug</u>. Event is still ongoing.</p>
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13.3.9 GI DISORDERS SOC. Listings and narratives of SAE & AE dropouts

Patients with events of “colitis” in Total DAC database, SUR.

USUBJID	AE CODE	Serious	Action	rel Day	Outcome
203/365-002	CROHN'S DISEASE	N	DRUG WD	1636	NOT RESOLVED
203/454-006	COLITIS ULCERATIVE	N	DOSE INTERR	1674	
201/454-007	CROHN'S DISEASE	Y	NONE	354	NOT RESOLVED
202/502-006	COLITIS ULCERATIVE	Y	DRUG WD	555	
202/502-006	COLITIS ULCERATIVE	Y	NONE	584	
203/505-011	COLITIS	Y	NONE	1161	
203/505-011	COLITIS	Y	DRUG WD	1208	NOT RESOLVED
202/505-014	COLITIS ULCERATIVE	N	DRUG WD	650	NOT RESOLVED
203/505-026	COLITIS	N	DRUG WD	1301	
203/505-026	COLITIS ULCERATIVE	Y	NONE	1551	NOT RESOLVED
203/506-012	COLITIS ULCERATIVE	Y	DOSE INTERR	794	
203/506-012	COLITIS ULCERATIVE	N	NONE	824	NOT RESOLVED
203/556-001	ENTEROCOLITIS HAEMORRHAGIC	Y	NONE	1047	
203/559-002	COLITIS	N	DRUG WD	832	
203/559-002	CROHN'S DISEASE	N	NONE	940	NOT RESOLVED
203/566-001	COLITIS ULCERATIVE	N	DRUG WD	1487	
203/758-028	COLITIS ULCERATIVE	N	NONE	1247	
203/758-028	COLITIS ULCERATIVE	Y	NONE	1254	
203/758-028	COLITIS ULCERATIVE	N	NONE	1269	NOT RESOLVED
203/759-006	CROHN'S DISEASE	Y	DOSE INTERR	377	
203/759-006	CROHN'S DISEASE	N	NONE	393	NOT RESOLVED

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303/102-009	COLITIS	N	DOSE INTERR	462	NOT RESOLVED
303/102-009	PROCTITIS	N	DOSE INTERR	462	NOT RESOLVED
303/130-005	COLITIS MICROSCOPIC	N	NONE	189	
303/144-002	COLITIS	N	NONE	968	
301/156-003	COLITIS MICROSCOPIC	Y	DOSE INTERR	193	
301/156-003	COLITIS	N	DRUG WD	288	
301/165-002	COLITIS	N	NONE	774	
303/165-002	COLITIS MICROSCOPIC	N	DRUG WD	1160	
303/327-005	COLITIS MICROSCOPIC	N	NONE	1008	NOT RESOLVED
303/411-003	COLITIS	N	NONE	486	NOT RESOLVED
301/453-038	COLITIS ULCERATIVE	Y	NONE	429	
301/453-038	COLITIS ULCERATIVE	Y	DRUG WD	708	
303/606-010	COLITIS	Y	DOSE INTERR	1119	
303/611-012	COLITIS ULCERATIVE	Y	DRUG WD	375	NOT RESOLVED
303/611-038	PROCTOCOLITIS	N	NONE	974	
303/614-037	PROCTITIS	N	NONE	710	NOT RESOLVED
301/658-001	INFLAMMATORY BOWEL DISEASE	N	NONE	792	
302/101-101	COLITIS	N	NONE	89	

An additional SAE of Crohn's Disease (303/539-010*) submitted after cut-off of SUR

Of note, an empty space does not necessarily mean that an event resolved. It means that there is an end data for the event in the dataset, but if the patient is still receiving treatment the event should not be considered resolved. To go back to Section 8.5.3 click (8.5.3).

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Listings/narratives of SAE in GI SOC

Listing of selected SAE in the Gastrointestinal Disorders SOC in Studies 201 and 301

ID	PT Comment
Study 301 (DAC HYP 150)	
301/ 156-003	COLITIS MICROSCOPIC (<i>with vasculitic rash</i>). 39 M. On Day 193 to 227. Drug Withdrawn. Preceded by SAE transient lymphopenia day 172, had diarrhea after 7 doses of DAC. Drug interrupted (last dose prior to interruption was on Day 168); restarted Day 241 after resolution of diarrhea and colitis. Received 2 more doses and discontinued permanently because of recurrent colitis . Last dose of DAC was on Day 284 (a total of 9 doses). MS relapse treated with IVPM x3days, starting Day 236. On Day 344 (almost 2 months after discontinuation) dermal papules treated with acyclovir. On Day 345 seen by dermatologist, worsening, progressing, treated with prednisone 40 mg x 5 days and 20 mg po for 4 days. Skin biopsy showed vasculitic skin rash , reported as resolved on Day 358. <i>No evidence of infection. Colitis and vasculitis could be related to study drug.</i>
301/ 453-038	COLITIS ULCERATIVE (2 episodes). 19 M. Day 429-454, and 708-721. Colitis ulcerative diagnosed by colonoscopy. First episode after 16 doses of DAC150. Started mesalazine day 447 also had a few days of betamethasone. Second episode led to drug WD. Last dose of DAC was on Day 700 (total of 16 doses of DAC150). Treated with Cipro, metronidazole and started treatment with prednisone. No other AE reported. WBC elevated at week 96 (Day 673) FU visit 1: Labs atypical lymphocytes day 750. Unclear how long prednisone treatment was.
301/ 554-009	ANAL FISTULA. 41 F. Event started as a non-serious AE on day 419 and was “upgraded” to a SAE on Days 637 to 677, described as “complete transsphincteric anal fistula.” Patient also had recurrent genital herpes, oral herpes and allergic dermatitis. Drug Interrupted but continued. Alternative IFN alfa-2b was started without discontinuing DAC HYP on Day 441.
301/ 161-004	ENTEROCOLITIS. 53F. This SAE was of moderate intensity. DAC150 continued for a total of 35 doses. Patient had several AEs: lymphadenopathy on Days 66-84, pneumonia Days 76-79, intermittent rash Days 265 to 769, mild elevated platelets started Day 253 (not resolved), GI infection Day 280 (after 11 doses of DAC150), intestinal polyp on Day 650, erosive gastritis Days 721-726; colitis Days 632-637 (after a total of 22 doses); gastroenteritis viral 946-1009. Also had joint swelling Days 504-670, and a SAE of toxic encephalopathy Day 510-513 treated with VitB12 and folic acid. Local swelling left leg Day 940-943. Swelling right hand Day 947-961. Increased WBC, lymphocytes, neutrophils weeks 72, 84, 96. Intermittent use of various antibiotics, antidiarrheal, analgesics. <i>Complex case, recurrent gastroenteritis/colitis, transient lymphadenopathy, rash, arthritis and encephalopathy. Confounded by use</i>

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	<i>of multiple antibiotics and analgesics. Perhaps infectious or immune mediated. Incomplete workup (No ANA or workup for celiac Dz or Whipple’s). No mention of colonoscopy in this patient. (Not included in analysis of “colitis”)</i>
202/ 502-006.	COLITIS ULCERATIVE (two episodes) 21 M. SAE of severe intensity, on DAC 300. Drug withdrawn. Received 13 doses of DAC 300 in 201. Developed seborrheic dermatitis and erosive duodenitis during 201. In study 202, 20 days after the 6 th dose in 202 had dx of <u>ulcerative colitis</u> leading to WD. He had bloating, abd pain and <u>diarrhea for 2 months</u> and fresh blood in stools for 1 mo. Base visit in 202 (12/14/2009) had rash on both upper arms, rubor of face (“skin dermatitis post steroid therapy”). On Day 56, mild rash on upper arm; week 20 (May 4): abdominal pain. On (b) (6) started having fever up to 40C. Then, hospitalized for UC, dehydration and abdominal pain edematous lower legs. Sigmoidoscopy (b) (6) confirmed Ulcerative Colitis . He had anemia HT 26% (normal 40-45%) increased platelets, low total protein, elevated CRP. Treated with mesalazine, metronidazole, antibiotics electrolytes, transfusion of PRBC, FFP, oral prednisone and azathioprine , with improvement after 1 month. Another episode requiring hospitalization on (b) (6) treated with IVMP sulfasalazine, antibiotics, fluids. Event reported as resolved after 11 days. <u>Withdrawn from study.</u>
203/ 501-013	DIARRHOEA “ENTERITIS” 35 F. Moderate. Received placebo in study 201; DAC 150 in 202 and 203. No action taken with drug. Seborrheic dermatitis Days 400-415. ALT elevation DAC Day 422-505 (<2xULN). Diarrhea reported Day 847 to 856. Enteritis reported Day 478-975. Episode of giardiasis reported Day 701-761. Colonoscopy on DAC Day 949: “enteritis”. <i>Confounded by Giardia infection. This patient was later diagnosed with C difficile colitis.</i>
203/ 505-011	COLITIS (possible UC) & dermatitis 36 F. Two episodes. Received DAC 300 in study 201; placebo/DAC 300 in 202, and DAC 150 in 303. Diagnosed with colitis after 16 doses of DAC in study 203. Drug continued. She had recurrent herpes labialis and aphthous stomatitis during studies 201/202 treated with acyclovir, and microcytic anemia that resolved by the end of 201. Intermittent treatment with NSAIDs & APAP in 201/202 for back pain. “Retroviral infection” on Day 110-117 in study 201. AE of dermatitis allergic in 201 and 202 treated with topical treatment and IV steroids. Intermittent diarrhea started in 203, Day 409; diarrhea and dehydration, dx as colitis on Day 433 (Colonoscopy large lesions from overlapping ulcers and inflammatory lesions in entire intestine less prominent on anus and rectum). Possible Ulcerative Colitis. Treated with fluids and mesalazine. Another event causing hospitalization on Day 503 (with diselectrolytemia and anemia) treated with metronidazole, iv dexamethasone and sulfasalazine, followed by oral dexamethasone. Resolved. Treatment permanently discontinued due to colitis after a total of 38 doses of DAC (last dose was in July 2012, Day

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	<p>450 of study 203). Stool culture grew several pathogenic organisms. Early termination visit was September 2012 (Day 513). Another episode one month later was treated with azathioprine, mesalazine and oral methylprednisolone. In (b) (6) hospitalized with increased liver enzymes, mostly GGT of 462, ALT <3xULN, normal BR; GGT peaked (b) (6) Liver enzyme elevation considered resolved (b) (6) Low lymph count in 203 at early term visit. At safety fu visit day 618: Low HTC, high WBC (15.6×10^9 /L, 82% neutrophils), blood urine present >150/hfp with trace protein and mucus (UTI?). Liver enzymes normal in 201/202. ALT and ALK P elevated on Day 567 (ALT 2xULN) but normal at last fu visit on Day 618. TSH low at week 20 in study 202. ANTI DAC AB negative in studies 201 and 203; positive in study 202 at weeks 12, 20 and 40 (weeks 12 and 20 a value of 46.6 is provided; for week 40 is “positive”) and negative at weeks 32 and 52. Neutralizing abs to DAC were negative. <i>Inflammatory colitis and dermatitis requiring prolonged immunosuppressive therapy. As per follow up information submitted in September 2015, the event of colitis was still ongoing >3 years after the last dose of DAC.</i></p>
<p>203/ 506-012</p>	<p>COLITIS ULCERATIVE (Later developed Hepatitis C) 45 F. Severe ulcerative colitis characterized by bloody diarrhea. On day 794 to 823, after a total of 29 doses of DAC 150. Drug interrupted, but eventually discontinued. Event preceded by thrombocytopenia in studies 201/202. A month after colonoscopic diagnosis of colitis she developed pleural effusion (thought to be infectious), decreased ejection fraction (45%) and mitral and tricuspid valve regurgitation and hyperglycemia. She was very sick, received multiple antibiotics, corticosteroids and mesalazine, as well as electrolyte replacement and blood transfusion. She later had ALT elevation up to 38xULN and was found to have positive Hepatitis C RNA testing. <i>UC was associated with other potential immune mediated disorders: thrombocytopenia, heart failure and hyperglycemia (although hyperglycemia could also had been secondary to corticosteroid treatment). There are no glucose measurements in this narrative/profile. There is no follow up of liver enzymes until recovery.</i></p>
<p>203/ 556-001</p>	<p>ENTEROCOLITIS HAEMORRHAGIC (<i>also had acute pancreatitis</i>) 20 F. Severe, on Days 1047 to 1057 after 25 doses in 203. Patient received DAC 150 except period of washout placebo in 202. No action taken. Event associated with acute pancreatitis. Bloody diarrhea painful cramps on lower abdomen day 673. Abd us incidental ovarian cyst. Negative stool cultures. Hospitalized for fu, ESR 46, CRP also elevated, amylase 367 (nl < 115 U/L) lipase 1644 (nl < 490 IU/L) with mild acute pancreatitis. Enterocolitis resolved on day 693 of study 203. Pt completed study continued on drug until Dec 2013 (total of 59 doses of DAC). No mention of colonoscopy or immunosuppressor treatment. <i>Unclear if this was infectious or immune mediated.</i></p>
<p>203/ 758-028</p>	<p>COLITIS ULCERATIVE (<i>also had chronic pancreatitis</i>) 36 F. Moderate. On Days 1254 to 1269. Drug WD. Received DAC 150 x13, x13 and x19 (Total 45 doses). Onset Day 532 of</p>

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	<p>study 203. Day 510 Epigastric pain and bloody stools after treatment with amoxicillin for treatment of bronchitis. Colonoscopy was consistent with UC. Treatment included mesalazine. Diagnosed with chronic cholecystitis, chronic pancreatitis, gastroduodenitis. Treatment included IV prednisolone, Cipro, fluconazole, metronidazole. SAE of UC reported as resolved on Day 532 (b) (6) but non-serious AE of UC, chronic cholecystitis and pancreatitis were Not Resolved. Action is reported as “No action taken with drug “but she was LOST TO FOLLOW UP. (Last dose was July 17 2013.)</p>
<p>203/ 759-006</p>	<p>CROHN’S DISEASE (<i>withdrawn for ALT>30xULN after one more dose</i>) 39 F. On day 377 to 392, reported as “mild”. Pt had received placebo in 201; 13 of DAC 300 in 202, and DAC 150 in 203. (b) (6) (while in study 202, unknown date) chronic no specific colitis. LFTs were normal. In (b) (6) (after the first dose of DAC150 in study 203, total of 14 doses of DAC) she was hospitalized with diagnosis of Crohn’s disease and treated with metronidazole, sulfasalazine and metoclopramide. SAE was considered resolved (b) (6), but a non-SAE of Crohn’s remained ongoing, treated with mesalazine. On Day 34 of study 203 ALT was 30x ULN, AST 17xULN. BR and ALP were normal. Subject withdrew from the study because of liver enzyme elevation and Crohn’s, after a total of 15 doses of DAC. (<i>There is very little information in this narrative. Could this be some autoimmune liver disease? No further information on workup or outcome of liver event.</i>)</p>
<p>303/ 606-010</p>	<p>COLITIS (associated with erythema nodosum and lymphadenopathy). 23 F. Pt had at least 4 episodes of SAE MS relapse after 1, 6, 17, and 25 doses of DAC150. Erythema around both ankles (non-serious) after dose #30. At this time patient was taking carbamazepine, ferrous sulfate and naproxen. Erythema resolved day 857 of study 301. Colitis occurred in study 303, after 4 doses of DAC (day 97 in study 303). She had received a total of 36 doses. Hospitalized with 2-month history of diarrhea and lower abd pain. Labs showed anemia; other labs wnl. Colonoscopy: inflamat lesions and small erosions in distal part of rectum. Bx: non-specific chronic active inflammation. UC could not be rule out. Treated with mesalazine and Cipro. Event reported as resolved on Day 152, but patient continued on mesalazine. Most recent dose was October 24, 2014. Unclear for how long mesalazine was needed. As per datasets drug was interrupted.</p>
<p>303/ 613-005</p>	<p>PANCREATITIS (also allergic dermatitis). 30 F. Severe. Received IFNβ1a in 301. Had AE of MS relapse, urticaria and diabetes mellitus during 301. On Day 69 of study 303 (after 3 doses of DAC HYP), she had SAE of acute pancreatitis. The day before the event she was taken oxybutynin, gynalgin, drotaverine, norfloxacin. She was hospitalized with intense abdominal pain, vomiting and fever. Abdominal US was within normal limits. Labs showed lipase of 1260 U/L (normal 0-67 U/L). A gastroscopy showed erythematous gastritis with aphthous erosions. DAC was interrupted. She improved with diet and pharmacologic treatment. Event of pancreatitis resolved on Day 73 and did not reappear</p>

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	after the study treatment was <u>restarted</u> . However, the patient had an episode of MS relapse and allergic dermatitis after 10 doses of DAC and withdrew consent because she was disappointed with the lack of efficacy and the adverse events she was experiencing (<i>she also had “vaginal blastomycosis” and oxuriasis</i>). <i>The episode of acute pancreatitis could be unrelated to study drug.</i>
303/ 539-010 *	Crohn’s disease (IND safety report submitted after cutoff of SUR). 26 M with history of gastroduodenitis and duodenal ulcer was hospitalized due to bloody diarrhea and fever about 18 months after starting Daclizumab HYP in 303. Had received IFNβ1a in 301. On (b) (6) developed asthenia and fever. On (b) (6) the subject’s diarrhea became severe and bloody. On (b) (6) subject was admitted to the hospital where Crohn’s disease with duodenum involvement was suspected. Diagnostic tests performed (b) (6) included gastroscopy, duodenoscopy and bowel ultrasound (results currently not available). At the time of the last report the subject remained hospitalized.
303/ 439-007	Pernicious anemia. 38 F. Hx of allergy to metals. Dose interrupted. Dx of pernicious anemia made on Day 176, after 7 doses of DAC. Pt had received IFNβ1a in 301. Concom meds were amantadine, levocarnitine, paracetamol and vitamins. In (b) (6) she complained of fatigue and was found to have low Hg (6.9 g/dl (ref 12 to 16 mg/dl) with MCV of 119.5 (ref 80 to 100) and RDW 20.9% (ref <16%). RBC showed ovalocytes and schizocytes. Direct Coombs and anti C4d tests were negative. LDH was 8xULN. On (b) (6) she was assessed for anemia. Bone marrow aspiration (b) (6) suggested a vitamin deficiency with megaloblastosis without dysplasia. She had positive anti-gastric parietal antibodies. A histologic examination of fundal biopsy showed chronic atrophic autoimmune gastritis . SAE considered SEVERE. Treated with cyanocobalamine and vit B12. In (b) (6) (Day 254) she had elevated BR 2x ULN. Her most recent dose of DAC was (b) (6) (Day 219). Pernicious anemia reported resolved on Day 227. Drug was continued. BR remained elevated for remaining of study. ALT/AST/GGT and ALP were generally within normal. BR normalized by December 2014. Apparently patient still on study.

Source: ADAE3 dataset. SUR.

“Listing of Non-SAE DROPOUTS IN GI DISORDERS

301/ 593-001	35 F. Developed recurrent cheilitis and gingivitis Day 160 to 256, leading to dose interruption. Also had “plicated tongue” of moderate intensity on Day 223, after 8 doses of DAC HYP 150. Event resolved after one month but patient withdrew consent. Dac antibody positive (titer of 60) on Day 169, and negative at other time points.
202/ 505-014	24 F colitis ulcerative of mild intensity on Day 650 after 25 doses of DAC HYP 300. Nasopharyngitis, influenza, fatigue, MS relapse, rotaviral diarrhea, arthralgia, recurrent diarrhea Days 240 to 288 of study 202.

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	On day 286 of study 202 diagnosed with Ulcerative colitis (by colonoscopy). The event led to withdrawal and is reported as not resolved. Treated with mesalazine, rifampin, prednisone 40 mg with taper to 5 mg/day from Day 349 to Day 439 of study 202. She also had an anal fissure on day 473 to 494. Patient weighted 63 kg at baseline on 201, and 51 kg by week 52 of study 202. <i>(12 kg weight loss over 2 year period)</i>
202/ 758-016	45 F, diagnosed with pancreatitis of moderate intensity on Day 313, after 16 doses of DAC 150. The event resolved 2 months later.
203/ 306-001	43 F received DAC 300 in study 201, placebo and DAC 300 in 202 and DAC 150 in study 203. She developed Lip swelling, edema of the mouth of moderate intensity along with lymphadenopathy after a total of 82 doses of DAC HYP. She also had lip dyskeratosis and eczema after 20 and 36 doses of DAC, respectively. A drug reaction was suspected. DAC was discontinued. Treatment included oral prednisolone. The events of mouth edema, generalized rash resolved 4 months after drug discontinuation. Duration and dose of prednisone dose not stated. Lymphadenopathy did not resolve. <i>This event is consistent with an allergic reaction (RASH, LYMPHADENOPATHY & FACIALEDEMA).</i>
203/ 365-002	40 F, diagnosed with Crohn's disease of moderate intensity on Day 1636 after 53 doses of DAC. She received DACHYP 300 in 301, placebo and DAC 300 in 202 and DAC 150 in 203. Reported as not resolved. During 201/202 she had urinary infections, recurrent nasopharyngitis, glaucoma. In 202 diagnosed with polyarteritis nodosa/ panarteritis nodulosa cutanea benigna (Day 652-696, dose interrupted). In 203 she presented viral gastroenteritis, nor cardiac chest pain, vomiting, swollen legs. Starting on Day 1490 presented recurrent diarrhea and abdominal pain, later diagnosed as Crohns by colonoscopy on Day 1636. Details of the diagnosis are not provided. Treated with prednisolone 60 mg/day with taper to 5 mg/day from Day 1662 to 1719. Event ongoing at the time of last follow up. The patient withdrew from the study. Weight at screening to 201 was 72 kg. By the end of 201 she weighed 80 kg, by end of 202 she weighed 86 kg and by the final safety follow up (day 1776) she weighed 102 kg. <i>(probably because all the corticosteroids she received).</i>
203/ 559-002	21 F received DAC 300 in 201, placebo and DAC 300 in 202 and DAC HYP 150 in study 203. She was diagnosed with Colitis of mild intensity on Day 832 after 30 doses of DAC, later diagnosed as Crohn's disease. Details of the diagnosis are not provided. Event of colitis reported as resolved after 3 months. The patient also had ALT/AST elevation 5xULN at the time of Dx of Crohn's disease. Treatment included azathioprine, mesalazine and oral methylprednisolone. ALT/AST elevation resolved after 3 weeks. Event of Crohn's did not resolve. Weight at screening to 201: 45 kg, by end of 202 and 203 (week 144) it was 41 kg.

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303/ 165-002	27 F diagnosed with colitis microscopic of moderate intensity on Day 1160 after 41 doses of DAC HYP 150. During 301 had episodes of diarrhea, arthralgia, GERD, dizziness, facial flushing, fatigue, cholecystitis, respiratory infection, colitis, fatigue, MS relapse. In 303 had urinary and fecal incontinence, muscle spasticity, diarrhea and fall. She also had significant tooth decay/caries and required extraction of several teeth and molars. Colitis microscopic/lymphocytic colitis was diagnosed on Day 1160 and resolved on Day 1231, led to drug withdrawal, was treated with budesonide and resolved after approx. 2 months. Weight at screening to 301 was 103 kg; at the end of 301 it was 97 kg. <i>(This is the second case of colitis microscopic in this application, the other was in study 301 in a different patient)</i>
203/ 508-021	44 F developed constipation and proctalgia of moderate intensity after first dose of DAC HYP 150 in study 203. She received DAC 300 in study 201, placebo and DAC 300 in 202 and DAC 150 in 203 (total of 32 doses). Proctalgia did not resolve. Patient was eventually diagnosed with carcinoma of the anus after 5 additional doses of DAC. DAC was discontinued. She had no hx of genital warts or HPV infection. Testing for HPV and sexual history not reported. She was treated with chemotherapy. Event was ongoing at time of last follow up. Patient withdrew from the study.
303/ 167-002	53 F, history of hypothyroidism. She had one transient episode of diarrhea in 301. Then, recurrent diarrhea of mild intensity in 303 on Day 841, after a total of 34 doses of DAC 150. Treated with loperamida and rifaximin. Event did not resolve. DAC discontinued. Patient withdrew from the study. Weight at entry to 301 was 105 kg; by the end of 301/first day of 303 it was 95 kg. (10 kg weight loss over a 2-year period). No further weight measurements.

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13.3.9.1. GI inflammatory conditions by HLGT and HLT in Study 301 are shown below (JumpStart analyses done with MedDRA at a Glance)

System Organ Class	High-Level Group Term	High-Level Term	Preferred Term	DME	Signal	Signal At			Treatment:		Control:		Risk Difference
						SOC	HLGT	HLT	150 mg DAC HYP and Avonex placebo N=919		30 ug Avonex and DAC HYP placebo N=922		
									Subject Count	%	Subject Count	%	
Gastrointestinal disorders	Gastrointestinal inflammatory con	Colitis (excl infective)						7	0.8	0	0.0	0.8	
Gastrointestinal disorders	Gastrointestinal inflammatory con	Colitis (excl infective)	Colitis					4	0.4	0	0.0	0.4	
Gastrointestinal disorders	Gastrointestinal inflammatory con	Colitis (excl infective)	Colitis microscopic					2	0.2	0	0.0	0.2	
Gastrointestinal disorders	Gastrointestinal inflammatory con	Colitis (excl infective)	Colitis ulcerative					1	0.1	0	0.0	0.1	
Gastrointestinal disorders	Gastrointestinal inflammatory con	Colitis (excl infective)	Inflammatory bowel disease					1	0.1	0	0.0	0.1	
Gastrointestinal disorders	Gastrointestinal inflammatory con	Gastritis (excl infective)						16	1.7	19	2.1	-0.3	
Gastrointestinal disorders	Gastrointestinal inflammatory con	Gastritis (excl infective)	Gastritis					15	1.6	18	2.0	-0.3	
Gastrointestinal disorders	Gastrointestinal inflammatory con	Gastritis (excl infective)	Gastroduodenitis					1	0.1	1	0.1	0.0	
Gastrointestinal disorders	Gastrointestinal inflammatory con	Gastrointestinal inflammatory disorders NEC						6	0.7	0	0.0	0.7	
Gastrointestinal disorders	Gastrointestinal inflammatory con	Gastrointestinal inflammatory dis	Duodenitis					1	0.1	0	0.0	0.1	
Gastrointestinal disorders	Gastrointestinal inflammatory con	Gastrointestinal inflammatory dis	Enteritis					1	0.1	0	0.0	0.1	
Gastrointestinal disorders	Gastrointestinal inflammatory con	Gastrointestinal inflammatory dis	Enterocolitis					4	0.4	0	0.0	0.4	
Gastrointestinal disorders	Gastrointestinal inflammatory con	Oesophagitis (excl infective)						1	0.1	2	0.2	-0.1	
Gastrointestinal disorders	Gastrointestinal inflammatory con	Oesophagitis (excl infective)	Oesophagitis					1	0.1	2	0.2	-0.1	
Gastrointestinal disorders	Gastrointestinal inflammatory con	Rectal inflammations NEC						2	0.2	0	0.0	0.2	
Gastrointestinal disorders	Gastrointestinal inflammatory con	Rectal inflammations NEC	Proctitis					1	0.1	0	0.0	0.1	
Gastrointestinal disorders	Gastrointestinal inflammatory con	Rectal inflammations NEC	Proctocolitis					1	0.1	0	0.0	0.1	

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13.3.10 IMMUNE MEDIATED REACTIONS

On February 18, 2016, the DNP asked Biogen to submit AE datasets for patients who had potential immune related disorders (as per preferred terms listed below, plus any skin and angioedema type reaction that they considered immune related).

Table 13.3.10.1 List of PT for potential immune mediated events in study in DAC HYP

Adrenal insufficiency	Inflam Bowel Dz	Sialoadenitis
Alopecia areata	Iridocyclitis	Splenomegaly
Alveolitis	Iritis	Spondyloarthropathy
Ankylosing spondylitis	Leukocytoclastic vasculitis	Synovitis
Anti thyroid antibody positive	Lupus-like syndrome	Systemic lupus erythem.
Aphthous stomatitis	Morphea	Thrombocytopenia
Asthma	Myasthenia gravis	thyroiditis
Atypical pneumonia	Myositis	Type 1 diabetes mellitus
Autoimmune hepatitis	Pancreatitis	Uveitis
Autoimmune thyroiditis	Parapsoriasis	Vasculitis
Basedow's	Parotid gland enlargement	Vitiligo
Blood thyroxine decreased	Parotitis	
Blood thyroxine increased	Periarteritis nodosa	
Blood TSH decreased #	Pericarditis	
Blood TSH increased #	Pernicious anemia	
Celiac disease	Platelet count decreased	
Chronic hepatitis	Pneumonitis	
Colitis	Primary hypothyroidism	
Colitis microscopic	Proctitis	
Colitis ulcerative	Proctocolitis	
Crohn's disease	Proteinuria	
Cutaneous lupus erythematosus	Psoriasis	
Cutaneous sarcoidosis	Pulmonary fibrosis	
Diabetic ketoacidosis	Pulmonary granuloma	
Drug reaction with eosinophilia and SS	Pulmonary sarcoidosis#	
Enteritis	Pustular psoriasis	
Enterocolitis	Reiter's syndrome	
Erythrodermic psoriasis	Reynaud's phenomenon	
Goitre	Rheumatoid arthritis	
Guttate psoriasis	Sarcoidosis	
Hyperthyroidism	Scleritis	
Hypothyroidism	Seronegative arthritis	

Additional information regarding number of doses of DAC received, treatment and updated outcomes was also required for those events. A response was submitted on 3/8/16.

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13.3.10.2 PT included in Customized
MedDRA Query dated 3/14/16.

Acute hepatic failure	Enterocolitis
Adrenal insufficiency	Enterocolitis haemorrhagic
Alopecia areata	Erythema multiforme
Alveolitis	Erythema nodosum
Angioedema	Erythema nodosum
Ankylosing spondylitis	Erythrodermic psoriasis
Anti-thyroid antibody positive	Erythrodermic psoriasis
Aphthous stomatitis	Glomerulonephritis
Asthma	Glucose tolerance decreased
Atypical pneumonia	Glucose tolerance impaired
Autoimmune hepatitis	Glucose urine present
Autoimmune thyroiditis	Glycosylated haemoglobin increased
Basedow's disease	Goitre
Blood thyroid stimulating hormone decreased	Guttate psoriasis
Blood thyroid stimulating hormone increased	Haemolytic anaemia
Chronic hepatitis	Histiocytosis haematophagic
Coeliac disease	Hyperglycaemia
Colitis	Hypersensitivity
Colitis microscopic	Hyperthyroidism
Colitis ulcerative	Hypothyroidism
Crohn's disease	Inflammatory bowel disease
Cutaneous lupus erythematosus	Interstitial lung disease
Cutaneous sarcoidosis	Iridocyclitis
Dermatitis allergic	Iritis
Dermatitis atopic	Leukocytoclastic vasculitis
Dermatitis bullous	Leukocytosis
Dermatitis psoriasiform	Lupus-like syndrome
Diabetes mellitus	Lymphadenitis
Diabetic ketoacidosis	Lymphadenopathy
Drug hypersensitivity	Lymphocyte count increased
Drug reaction with eosinophilia and systemic symptoms	Lymphocytosis
Eczema	Lymphoid tissue hyperplasia
Enteritis	Lymphoid tissue hyperplasia
Enteritis	Mesangioproliferative glomerulonephritis
Enterocolitis	Morphoea
	Mouth ulceration

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Myasthenia gravis

Myositis

Pancreatitis

Parapsoriasis

Parapsoriasis

Parotid gland enlargement

Parotitis

Pericarditis

Pernicious anaemia

Platelet count decreased

Platelet count increased

Pneumonitis

Polyarteritis nodosa

Polyarthrititis

Primary hypothyroidism

Proctitis

Proctocolitis

Proteinuria

Pruritus allergic

Psoriasis

Pulmonary fibrosis

Pulmonary granuloma

Pulmonary sarcoidosis

Pustular psoriasis

Rash macular

Rash maculo-papular

Rash papular

Rash pruritic

Raynaud's phenomenon

Reiter's syndrome

Rheumatoid arthritis

Sarcoidosis

Scleritis

Seronegative arthritis

Sialoadenitis

Splenomegaly

Spondyloarthropathy

Swelling face

Synovitis

Systemic lupus erythematosus

Thrombocytopenia

Thrombocytosis

Thyroiditis

Thyroxine decreased

Thyroxine increased

Toxic skin eruption

Type 1 diabetes mellitus

Urethritis noninfective

Urticaria

Uveitis

Vasculitis

Vitiligo

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13.3.10.3 Listing of patients with immune mediated conditions in the total DAC HYP database.

Of note, only hepatic events that were diagnosed as autoimmune hepatitis are included.

- **Blood and lymphatic**

Hemolytic Anemia (n=2) (SAE)

203/100-002* and 302/463-103*

Thrombocytopenia (n=4) (SAE)

SAEs 303/649-009*, 301/480-002, 301/617-003, 203/906-005.*

Hemophagocytic syndrome

203/303-005 (SAE)

Lymphadenopathy consistent with but not diagnosed as sarcoidosis (at least 3):

303/609-013*, 301/437-001 and 203/505-032*

- **Reported under Endocrine disorders**

Thyroid disease

201/752-012 Autoimmune thyroiditis (SAE)

301/327-005 thyrotoxicosis and ketoacidosis (Type I DM) (SAE)

202/765-003 chronic urticaria, Basedow's, goiter and chronic AIHepatitis (SAE) **

203/563-001 goiter and idiopathic pulmonary fibrosis (discussed under respiratory SOC (SAE)**

201/460-004 Autoimmune thyroiditis

202/501-014 Autoimmune thyroiditis

301/557-001 Autoimmune thyroiditis

301/624-004 Autoimmune thyroiditis

303/703-006 Basedow's disease

303/741-004 Basedow's disease

Type 1 DM

301/327-005 Thyrotoxicosis and ketoacidosis

303/667-017* Type1 DM, DILI, eczema and pancreatitis **

201/903-012 Diabetes insipidus (in site 903, probably on drug) SAE, could be hypophysitis.

The following cases require additional information

USUBJID	AECOD	Serious	ACTION	Start Day	Outcome	Total DAC
202/102-001	BLOOD GLUCOSE INCREASED	N	NONE	57		33
203/301-004	BLOOD GLUCOSE INCREASED	N	NONE	1715		62
203/306-002	BLOOD GLUCOSE INCREASED	N	NONE	778	NOT RESOLV	32
201/363-004	GLYCOSYLATED HAEMOGLOBIN IN	N	NONE	147		26
203/506-012	BLOOD GLUCOSE INCREASED	N	NONE	729		31
202/768-007	BLOOD GLUCOSE INCREASED	N	NONE	420		58
202/768-007	BLOOD GLUCOSE INCREASED	N	NONE	503		58
202/768-007	BLOOD GLUCOSE INCREASED	N	NONE	589		58
301/327-005	BLOOD GLUCOSE INCREASED	N	NONE	877		41
302/152-502	BLOOD GLUCOSE INCREASED	N	NONE	99	NOT RESOLV	17

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There was no narrative and no glucose measurements. The applicant should clarify if these patients developed hyperglycemia because of treatment with high dose steroids, and whether any of these patients had any other autoimmune process.

- **Reported under Eye disorders**

The following conditions are typically associated with sarcoidosis.

201 and 202/503-002 UVEITIS Day 233 -600

201 and 202/505-023 UVEITIS and IRITIS (SAE), recurrent, also recurrent pruritus, recurrent diarrhea.

303/441-013 UVEITIS Day 1114, not resolved

301/443-001 UVEITIS Day 745 to 785

303/609-008* Iritis (SAE). At time of event patient also had hypothyroidism) **

- **Under General disorders**

301/606-020 *Multiorgan failure (SAE) ***

303/453-048 *PYREXIA (SAE) suspected of brucellosis ***

303/609-013 *EDEMA PERIPHERAL (SAE) ***

I will include these cases along with the systemic inflammatory syndromes of unknown origin/multiorgan hypersensitivity.

- **Under Gastrointestinal disorders SOC**

COLITIS N=28, including 12 SAE. (Narratives in Section 13.3.9 of this review.)

PANCREATITIS - 12 cases of pancreatitis were reported as of the SUR (only one SAE and one leading to drug WD have narratives).

303/667-017* *Pacreatitits, Type 1 DM, eczema and DILI mentioned earlier (**)*

The cases of pancreatitis as of the SUR are listed below

USUBJID	AECOD	Ser	Action	Start Day	End Day	Outcome	Total DAC doses
203/556-001	PANCREATITIS ACUTE	N	NONE	1053	1064		59
201/751-007	PANCREATITIS	N	NONE	48	58		69
203/758-011	PANCREATITIS ACUTE	N	DOSE INTERRUPTED	1752	1759		69
202/758-016	PANCREATITIS	N	DOSE INTERRUPTED	9	228		3
202/758-016	PANCREATITIS	N	DRUG WITHDRAWN	313	372		3
203/758-028	PANCREATITIS CHRONIC	N	NONE	1254		NOT RESOLVED	47
203/763-020	PANCREATITIS CHRONIC	N	NONE	829		NOT RESOLVED	29
203/901-006	PANCREATITIS CHRONIC	N	DOSE INTERRUPTED	764		NOT RESOLVED	26
202/906-003	PANCREATITIS	N	NONE	461	469		65
202/913-006	PANCREATITIS CHRONIC	N	DOSE INTERRUPTED	552		NOT RESOLVED	16
303/611-012	PANCREATITIS ACUTE	N	NONE	431	445		14
303/613-005	PANCREATITIS	Y	DOSE INTERRUPTED	69	73		10
303/649-009	PANCREATITIS CHRONIC	N	NONE	164		NOT RESOLVED	4

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The event of pancreatitis reported in the patient who also had eczema, AIH and diabetes mellitus is clearly autoimmune and likely related to DAC HYP. It is consistent with IPEX syndrome or perhaps multiorgan hypersensitivity/DRESS.

Additional information is needed from other cases of pancreatitis to evaluate whether they are immune mediated or not, as well as whether they were associated with other autoimmune diseases and whether they required any treatment.

Other GI autoimmune diseases

303/439-007 PERNICIOUS ANEMIA (SAE)
303/141-008 CELIAC DISEASE (SAE)
303/203-005 CELIAC DISEASE
303/311-018 CELIAC DISEASE
303/611-012 CELIAC DISEASE (and ulcerative colitis)**

- **Under Hepatobiliary SOC**

Autoimmune hepatitis (n=7) SAE. *Some of the AIH had colitis, thrombocytopenia, thyroiditis were already counted.*

302/622-108 Primary biliary cirrhosis.
301/474-006 had ALT elevation, eosinophilia and +ASMA 1:40. *In my opinion consistent with immune mediated hepatitis.*
303/667-017* *eczema, DILI, Type 1 DM and pancreatitis (SAE)***

- **Under Immune system disorders**

303/611-029 PULM SARCOIDOSIS (SAE) - As per FU IND report 1/28/16 resolved 12/30/2016 (unclear if off meds).
302/463-105 PULM SARCOIDOSIS, not resolved
303/659-001 sarcoidosis, not resolved – also developed cerebral venous thrombosis.
301/659-014 sarcoidosis, not resolved
302/659 116* Cutaneous sarcoidosis
302/622-502* SARCOIDOSIS
203/555-001* SARCOIDOSIS in patient who presented with angioedema
303/622-106* Generalized lymphadenopathy/suspected sarcoidosis
203/555-001* Patient with recent dx of sarcoidosis had anaphylaxis

Additional cases highly suggestive of sarcoidosis, from Blood disorders SOC:

303/609-013* *LYMPHADENOPATHY (SAE) also exfoliative rash, edema, lung nodules)*

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301/437-001. ANAEMIA, LYMPHADENOPATHY (SAE) pulmonary micronodules and mediastinal lymphadenopathy

203/505-032* LYMPHADENOPATHY/lymphadenectomy (SAE) almost 5 years into treatment. suspected toxoplasma but IgM negative. Incomplete workup to rule out sarcoidosis.

Additional case highly suggestive of sarcoidosis from Infections SOC

303/301-010. (SAE). Had pneumonia during hospitalization for severe skin rash. CT scan consistent with either "pneumonitis" or a resolving consolidation. Small mediastinal nodes.

I am only counting the 9 cases that the applicant acknowledged (although they later disputed one). If I count the suspicious cases of sarcoidosis there would be at least 11 cases.

Systemic inflammatory responses of unknown origin consistent with SEPSIS OR Multiorgan hypersensitivity (DRESS)

301/606-020 (SAE)– Multiorgan failure. Reported under General disorders, under Infections (bacterial/viral/fungal) and also under Vascular system disorders ("Kawasaki syndrome" ANCA+ systemic vasculitis). Is also consistent with multiorgan hypersensitivity/DRESS. Treated with plasmapheresis. (Reported under General disorders and Infections SOC)

203/303-005 (SAE) – Hemophagocytic syndrome with catastrophic antiphospholipid antibody and septicemia . Multiorgan failure suspected of sepsis without source or organism. (The investigator reporting term was Macrophage Activating Syndrome) (reported under Blood and Infections)

303/552-001* PYREXIA (SAE) Fever and allergic reaction of unknown etiology with toxic damage to the liver, skin rash, interstitial change in lungs treated with prednisone and acyclovir.

303/645-015*. Adult Still's disease after 21 doses of DAC. Picks of fever and polyarthritis/sepsis- like picture. Treated with systemic corticosteroids.

303/453-048 PYREXIA (SAE) Multiorgan involvement including lung, liver, blood, lymphadenopathy, consistent with DRESS; no adequate evidence to support diagnosis of brucellosis based on serologic test of unknown specificity in a patient living in endemic area for Brucella) (Reported under General disorders and Infections)

303/609-013 EDEMA PERIPHERAL along with generalized eczema, lung disease and lymphadenopathy, suspected by investigator to have DRESS. There is little information about the edema event. *Case also consistent with sarcoidosis (Reported under General Disorders)*

203/901/006 Event of SJS reported by investigator. However, none of the dermatologists confirmed this diagnosis. He had multiple organ system involvement and diagnosed with "secondary immunodeficiency with autoimmune syndrome" with signs of skin and mucosa

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lesions consistent with DRESS. Treatment included IV dexamethasone and oral methylprednisolone. The subject withdrew from the study and there is no further follow up.

Reported under Skin SOC

I mention 303/667-017 eczema, DILI, Type 1 DM and pancreatitis in this group because I think it is consistent with multiple organ hypersensitivity reaction/DRESS but events occurred sequentially over a few months, and the patient had recovered from DILI at the time of the pancreatitis and Type 1 DM. The types of events are consistent with an IPEX syndrome. I am not including this in the count for systemic inflammatory response.*

- **Under Infections SOC**

Lung infections

Consistent with immune mediated lung disease: 303/ 611-049, 303/552-014 and 303/301-010.

Sepsis/fever of unknown origin (described under systemic inflammatory syndromes)

Kawasakis syndrome

HPS

Pyrexia - brucellosis

Other events reported under Infections, potentially immune mediated (Sjogren's syndrome?)

303/154-001 PAROTID GLAND ENLARGEMENT, D 873, no action, not resolved, (54 dos)

303/238-001 PAROTITIS (SAE) DAC interrupted, on D 959-969 (35 doses)

301/431-003 PAROTITIS (SAE) DAC interrupted, on D 663-721 (26 doses)

301/632-003 PAROTITIS on D 99-105 (39 doses)

- **Reported under Musculoskeletal and under Immune mediated disorders**

203/312-007 Morphea

301/148-004 Rheumatoid arthritis

302/463-107 Rheumatoid arthritis

303/645-015* Adult Still's disease (RA)

301/412-007 Systemic lupus Erythematosus

301/482-005 Lupus-like syndrome (SAE) (*also had nonSAE of Adrenal Insufficiency*)

303/658-012* Seronegative inflammatory polyarthritis

- **Reported under Nervous system Disorders**

303/600-010 Myastenia Gravis (SAE)

202/363 008 Aseptic meningitis (SAE)

301/133-004 Patient had headaches and underwent Temporal artery biopsy. Typically this biopsy is done to rule/out temporal arteritis, also known as Giant Cell arteritis, which is a form

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of vasculitis. There is no information about other symptoms that may have led the investigator to think about TA. The results of the biopsy are not included in the application.

- **Under Renal**

- 203/500-002 Glomerulonephritis (SAE), Segmental GN with nephrotic synd, not resolved
- 202/505-018 Glomerulonephritis (SAE), Mesangioprolif GN with nephrotic syndr, not resolved
- 303/649-009 *GN chronic (day 119) not resolved. In patient with AIH and thyroiditis. Upon request for additional information applicant stated that it was not confirmed without providing any more information.*
- 303/325-001* Renal sarcoidosis

- **Under Respiratory SOC**

- 203/563-001 recurrent alveolitis and idiopathic pulmonary fibrosis (cryptogenic fibrosing alveolitis with obliterate arteriopathy). (SAE)
- 301/457-001 Interstitial lung disease/interstitial pneumonia (SAE)
- 203/751-015 Interstitial lung disease, had “bilateral interstitial pneumonia” that resolved with sequela after antibiotic treatment (this could be sarcoid).
- 301/554-001 had an event coded as Pulmonary granuloma. Had miliary lung nodules and mediastinal lymphadenopathy.
- 303/ 611-049 (SAE). Interstitial lung disease/atypical pneumonia. Had ANCA+ fluorescence Type 1, granular. 1:320.

Additional potential case from infections: 303/552-014 (SAE) Polysegmental pneumonia, CT scan read as “hypersensitivity pneumonitis”

- **AE Reported under Skin and SC tissues (other than eczema, psoriasis and drug eruptions)**

Acute: 4 cases of vasculitis in study 301

ID	Dose	Code	Onset	End	Dur	Ser	Action	Outcome
205MS301/156-003	150 mg DAC HYP	VASCULIT	342	358	17	N	NONE	
205MS301/512-011	150 mg DAC HYP	LEUKOCYT	475	500	26	Y	DRUG WITHDRAWN	
205MS301/606-019	150 mg DAC HYP	VASCULIT	646	658	13	N	DRUG WITHDRAWN	
205MS301/660-008	150 mg DAC HYP	VASCULIT	246	253	8	N	DOSE INTERRUPTED	
205MS301/660-008	150 mg DAC HYP	VASCULIT	254	277	24	Y	DOSE INTERRUPTED	

Additional case of vasculitis in male patient diagnosed with breast cancer (303/115-006*)

Polyarteritis nodosa (in patient who also had Crohn’s disease, 202/365-002)

Panniculitis in patient who also had erythema nodosum (201/751-016)

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Non-acute skin reactions

201/100-002 ALOPECIA AREATA

203/453-011 Vitiligo

303/104-002 Vitiligo

303/603-003 Vitiligo

301/610-005 CUTANEOUS LUPUS ERYTHEMATOSUS (*doubt that this is cutaneous lupus,
I suspect sarcoidosis*)

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13.3.10.4

Preferred terms in Immune System Disorders SOC

Identified by MO in DAC HYP BLA as of February 2016.

- HL Allergic conditions
 - GT
 - HLT Allergic conditions NEC
 - HLT Allergies to foods, food additives, drugs and other chemicals
 - HLT Anaphylactic responses
 - HLT Angioedemas
 - HLT Atopic disorders
 - HLT Urticarias

- HL Autoimmune disorders
 - GT
 - HLT Autoimmune disorders NEC
 - HLT Blood autoimmune disorders
 - HLT Endocrine autoimmune disorders
 - HLT Hepatic autoimmune disorders
 - HLT Lupus erythematosus and associated conditions
 - HLT Muscular autoimmune disorders
 - HLT Nervous system autoimmune disorders
 - HLT Rheumatoid arthritis and associated conditions
 - HLT Scleroderma and associated disorders
 - HLT Skin autoimmune disorders NEC

Dermatitis allergic, dermatitis contact, dermatitis exfoliative, toxic skin eruption, erythema multiforme, panniculitis, hypersensitivity (*)
Drug eruption, drug hypersensitivity, Drug reaction with eosinophilia and systemic symptoms (DRESS)
Anaphylaxis
Angioedema, lip swelling, tongue swelling, periorbital edema, face edema
Dermatitis atopic
Urticarial rash

Celiac disease, pernicious anemia, Reiter's syndrome (Sjogren's syndrome)
Autoimmune hemolytic anemia, immune thrombocytopenia
Autoimmune thyroiditis, Basedow's, Type 1 DM
Autoimmune hepatitis, primary biliary cirrhosis
SLE, cutaneous lupus erythematosus, lupus-like syndrome
Myasthenia gravis, polymyalgia rheumatica,
Multiple sclerosis (**)
RA, autoimmune arthritis, Still's disease adult onset
Morphea
Alopecia areata, vitiligo, lichenoid reaction

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- HL
GT Immune disorders NEC
 - +...HLT Acute and chronic sarcoidosis
 - +...HLT Amyloidoses
 - +...HLT Autoinflammatory diseases
 - +...HLT Blood isoimmune reactions
 - +...HLT Immune and associated conditions NEC
- +...HLT Transplant rejections
- +...HLT Vasculitides

Sarcoidosis, pulmonary sarcoidosis, cutaneous sarcoidosis
Colitis ulcerative, Crohn's disease, erythema nodosum, glomerulonephritis, Hemophagocytic syndrome, Idiopathic pulmonary fibrosis, psoriasis, uveitis, iritis, sepsis syndrome, systemic inflammatory response
Cutaneous vasculitis, Kawasaki's disease, vasculitic rash

13.3.10.5 Analyses of Angioedema in this database.

The applicant used extensive splitting of events consistent with angioedema, such as lip swelling (under GI disorders), eye swelling (under Eye disorders), etc. I conducted a search for PTs that included the word swelling or edema in the AE dataset for study 301. Subsequently excluded terms that did not specifically refer to the face. That led me to a total of 45 events (23 on DAC150 (2.5%) and 11 on Avonex (1.2%).

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LISTING OF PATIENTS WITH AE CONSISTENT WITH ANGIOEDEMA in study 301

USUBJID	TRT	AETERM	AECOD	AEBODYSYS	Onset	End	Dur	Ser	Severity	Relation	ACTION	Outcome
205MS301/102-006	30 ug Avonex	DISCOMFORT SECONDARY TO BIL	LOCAL SWELLING	GENERAL DISORDERS AND A	189	197	9	N	MILD	NOT RELATE	NONE	
205MS301/126-008	30 ug Avonex	FACIAL SWELLING	SWELLING FACE	SKIN AND SUBCUTANEOUS	9	9	1	N	MODERAT	RELATED	NONE	
205MS301/176-007	30 ug Avonex	RIGHT SIDE OF FACE SWOLLEN	SWELLING FACE	SKIN AND SUBCUTANEOUS	71	78	8	N	MODERAT	NOT RELATE	NONE	
205MS301/300-009	30 ug Avonex	SWOLLEN AREA TO LEFT SIDE OF C	OEDEMA MOUTH	GASTROINTESTINAL DISORD	235	236	2	N	MILD	NOT RELATE	NONE	
205MS301/300-009	30 ug Avonex	SWOLLEN LIP SPREADING INTO CH	LIP SWELLING	GASTROINTESTINAL DISORD	415	416	2	N	MILD	NOT RELATE	NONE	
205MS301/412-009	30 ug Avonex	SWELLING LEFT LOWER LID	EYELID OEDEMA	EYE DISORDERS	449	478	30	N	MILD	NOT RELATE	NONE	
205MS301/613-014	30 ug Avonex	ALLERGIC REACTION ON FACE SKI	ALLERGIC OEDEMA	IMMUNE SYSTEM DISORDER	728	731	4	N	MODERAT	NOT RELATE	NONE	
205MS301/624-018	30 ug Avonex	SWELLING OF THE LOWER EYELID	EYELID OEDEMA	EYE DISORDERS	412	426	15	N	MILD	NOT RELATE	NONE	
205MS301/629-006	30 ug Avonex	FACE OEDEMA	FACE OEDEMA	GENERAL DISORDERS AND A	313	313	1	N	MILD	RELATED	DRUG WITHDRAWN	
205MS301/646-001	30 ug Avonex	EDEMA UNDER THE EYES	PERIORBITAL OEDEMA	EYE DISORDERS	106	260	155	N	MILD	NOT RELATE	NONE	
205MS301/646-001	30 ug Avonex	EDEMA EYELID	EYELID OEDEMA	EYE DISORDERS	523	562	40	N	MODERAT	NOT RELATE	NONE	
205MS301/657-006	30 ug Avonex	EDEMA OF LEFT LOWER JAW	FACE OEDEMA	GENERAL DISORDERS AND A	1035	1039	5	N	MODERAT	NOT RELATE	NONE	
205MS301/747-012	30 ug Avonex	GUM SWELLING	GINGIVAL SWELLING	GASTROINTESTINAL DISORD	263	268	6	N	MILD	NOT RELATE	NONE	
205MS301/101-011	150 mg DAC HYP	INTERMITTENT SWOLLEN LIPS	LIP SWELLING	GASTROINTESTINAL DISORD	219	320	102	N	MILD	NOT RELATE	NONE	
205MS301/101-011	150 mg DAC HYP	FACIAL SWELLING, INTERMITTENT	SWELLING FACE	SKIN AND SUBCUTANEOUS	380	381	2	N	MODERAT	NOT RELATE	NONE	
205MS301/101-011	150 mg DAC HYP	INTERMITTENT ANGIOEDEMA TO	ANGIOEDEMA	SKIN AND SUBCUTANEOUS	457	458	2	N	MILD	NOT RELATE	NONE	
205MS301/102-001	150 mg DAC HYP	UPPER LIP SWELLING	LIP SWELLING	GASTROINTESTINAL DISORD	760	788	29	N	MILD	NOT RELATE	NONE	
205MS301/123-002	150 mg DAC HYP	SWELLING ON FACE	SWELLING FACE	SKIN AND SUBCUTANEOUS	184	191	8	N	MODERAT	NOT RELATE	NONE	
205MS301/123-008	150 mg DAC HYP	SWOLLEN FEELING IN RIGHT SIDE	OEDEMA MOUTH	GASTROINTESTINAL DISORD	695	717	23	N	MILD	NOT RELATE	NONE	
205MS301/129-001	150 mg DAC HYP	RIGHT FACIAL SWELLING	SWELLING FACE	SKIN AND SUBCUTANEOUS	554	635	82	N	MODERAT	NOT RELATE	NONE	
205MS301/150-001	150 mg DAC HYP	GINGIVAL EDEMA-LEFT LOWER	GINGIVAL OEDEMA	GASTROINTESTINAL DISORD	236	248	13	N	MILD	NOT RELATE	NONE	
205MS301/161-006	150 mg DAC HYP	LOWER LIP SWELLING (ALLERGIC R	ALLERGIC OEDEMA	IMMUNE SYSTEM DISORDER	441	441	1	N	MODERAT	NOT RELATE	NONE	
205MS301/161-006	150 mg DAC HYP	UPPER LIP SWELLING ALLERGIC RE	ALLERGIC OEDEMA	IMMUNE SYSTEM DISORDER	567	568	2	N	MILD	NOT RELATE	NONE	
205MS301/161-006	150 mg DAC HYP	EYE SWELLING	EYE SWELLING	EYE DISORDERS	567	568	2	N	MILD	NOT RELATE	NONE	
205MS301/161-006	150 mg DAC HYP	INNER EAR SWELLING	EAR SWELLING	EAR AND LABYRINTH DISOR	756			N	MILD	NOT RELATE	NONE	
205MS301/162-002	150 mg DAC HYP	EDEMA FACE	FACE OEDEMA	GENERAL DISORDERS AND A	492			N	MILD	NOT RELATE	NONE	
205MS301/311-011	150 mg DAC HYP	CHRONIC IDIOPATHIC ANGIOEDEN	IDIOPATHIC ANGIOEE	SKIN AND SUBCUTANEOUS	721			N	MODERAT	NOT RELATE	NONE	
205MS301/327-005	150 mg DAC HYP	SWOLLEN EYELIDS	EYELID OEDEMA	EYE DISORDERS	698	711	14	N	MILD	NOT RELATE	NONE	
205MS301/431-003	150 mg DAC HYP	LIP EDEMA	LIP OEDEMA	GASTROINTESTINAL DISORD	295	298	4	N	MILD	NOT RELATE	NONE	
205MS301/432-001	150 mg DAC HYP	EYELID EDEMA	EYELID OEDEMA	EYE DISORDERS	462	516	55	N	MODERAT	NOT RELATE	NONE	
205MS301/441-021	150 mg DAC HYP	FACE ANGIOEDEMA WITH URTICA	ANGIOEDEMA	SKIN AND SUBCUTANEOUS	215	226	12	N	MODERAT	NOT RELATE	NONE	
205MS301/441-021	150 mg DAC HYP	FACE ANGIOEDEMA WITH URTICA	ANGIOEDEMA	SKIN AND SUBCUTANEOUS	226	286	61	Y	SEVERE	NOT RELATE	NONE	
205MS301/464-002	150 mg DAC HYP	EDEMA AT EYELID	EYELID OEDEMA	EYE DISORDERS	577	591	15	N	MODERAT	NOT RELATE	NONE	
205MS301/492-001	150 mg DAC HYP	MILD OEDEMA OF THE LEFT PREAL	LOCALISED OEDEMA	GENERAL DISORDERS AND A	775	874	100	N	MILD	NOT RELATE	NONE	
205MS301/552-014	150 mg DAC HYP	HYPERSENSITIVITY REACTION LIKE	ANGIOEDEMA	SKIN AND SUBCUTANEOUS	445	645	201	Y	MILD	RELATED	NONE	
205MS301/607-001	150 mg DAC HYP	FEELING OF THROAT OEDEMA	PHARYNGEAL OEDEM	RESPIRATORY, THORACIC AN	50	50	1	N	MILD	RELATED	NONE	
205MS301/607-001	150 mg DAC HYP	OEDEMA OF THROAT	PHARYNGEAL OEDEM	RESPIRATORY, THORACIC AN	50	51	2	N	MILD	NOT RELATE	NONE	
205MS301/607-001	150 mg DAC HYP	FEELING OF OEDEMA OF THROAT	PHARYNGEAL OEDEM	RESPIRATORY, THORACIC AN	85	86	2	N	MILD	RELATED	NONE	
205MS301/607-001	150 mg DAC HYP	SWELLING OF THE THROAT	PHARYNGEAL OEDEM	RESPIRATORY, THORACIC AN	394	397	4	N	MILD	RELATED	NONE	
205MS301/611-039	150 mg DAC HYP	OEDEMA OF EYE LIDS	EYELID OEDEMA	EYE DISORDERS	804	807	4	N	MODERAT	NOT RELATE	NONE	
205MS301/612-007	150 mg DAC HYP	BLEPHAREDEMA	EYELID OEDEMA	EYE DISORDERS	57	57	1	N	MILD	NOT RELATE	NONE	
205MS301/614-017	150 mg DAC HYP	SWELLING OF THE GUMS	GINGIVAL SWELLING	GASTROINTESTINAL DISORD	893	895	3	N	MILD	NOT RELATE	NONE	
205MS301/618-003	150 mg DAC HYP	SWELLING UPPER LIP	LIP SWELLING	GASTROINTESTINAL DISORD	841			N	MILD	NOT RELATE	NONE	
205MS301/622-009	150 mg DAC HYP	SWELLING OF THE EYELIDS	EYELID OEDEMA	EYE DISORDERS	900	966	67	N	MODERAT	NOT RELATE	NONE	
205MS301/703-004	150 mg DAC HYP	LOWER LIP SWELLING	LIP SWELLING	GASTROINTESTINAL DISORD	45	47	3	N	MODERAT	RELATED	NONE	

13.3.10.6 Additional analyses of immune mediated AEs from datasets submitted on 3/8/16

In response to a DNP request for information issued on 2/18/16, the applicant submitted datasets for patients with potential immune mediated reactions in the controlled studies and total DAC HYP database (as per a listing of PTs provided by DNP) on 3/8/16. These datasets included information on number of doses received before and after the immune reaction was diagnosed (which is a way of identifying if drug was stopped or not), the treatment received, whether the patient had a prior history of a similar event and the updated outcome.

Of note, determination of the preferred terms included in the analyses is of critical importance. The list provided by DNP on 2/18/16 did not include eczema and dermatitis (which in retrospect should have been included because although phenotypically different, in a series of cutaneous adverse events in multiple sclerosis patients treated with daclizumab they were histologically similar to DAC HYP induced psoriasiform rashes (47)). This list also missed potential cases of immune mediated hepatitis, because the only preferred term for this event was autoimmune hepatitis, and only 3 patients had been diagnosed as AIH in the SUR database (versus at least 11 cases of immune mediated hepatitis identified by FDA reviewers).²³ On the other hand, some events may have not been autoimmune (e.g. hyperthyroidism without workup that shows positive thyroid antibodies).

Therefore although the datasets submitted on 3/8/16 did not capture all potential immune mediated events, they provide important information for a substantial number of these events (e.g. psoriasis, colitis, lymphadenopathy) that was not available in the original datasets. These analyses are discussed below.

Overall, as per the applicant analyses, confirmed by this MO, the rate of potential immune mediated reactions as per the 2/18/16 list of terms was 17% for the Total DAC HYP database; in study 301, the rate was 18% on DAC150 vs. 6% on IFN β 1a, and in study 201, the rate was 7%, 8% and 3% in the DAC150, DAC300 and placebo groups, respectively.

Number of doses of DAC HYP received prior and after the immune mediated event

373 (17%) subjects presented 550 AE in the total DAC HYP database. Some presented more than one AE. Patients received a mean of 20 doses before the onset of the event (median 18, range 1 to 79) and a mean of 16 more doses after the event (median 10, range 0 to 80). As per

²³ Analyses of potential immune mediated hepatitis for other drugs (e.g. ipilimumab) have included any ALT>3xULN, which is probably too non-specific. An intermediate approach that could capture clinically relevant liver events could be to include all patients with liver enzyme in the biochemical Hy's law range (ALT>3x ULN and BR>2x ULN) along with cases with an ALT or AST elevation >10x ULN. Adding these events will require additional analyses.

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the original datasets, 50 of the 373 (13%) were withdrawn from treatment because of an immune mediated event. As per the 3/8/16 datasets 78 (21%) patients did not receive further doses after diagnosis and 52 (13%) received 1 or 2 more doses before stopping DAC HYP. Evaluation of most common immune mediated AE is shown below.

Rash

Psoriatic conditions

48 patients had psoriatic conditions including psoriasis, pustular psoriasis, guttate psoriasis, erythrodermic psoriasis and parapsoriasis. Of those, 9 had a prior history of psoriasis. Among these 9 patients, psoriasis or exacerbation of psoriasis occurred after a mean of 21 doses of DAC HYP (median 16, range 2 to 67). They received a mean of 26 additional doses after the diagnosis (median 26, range 0 to 57). Five of those 9 did not recover. One additional patient had a history of eczema. He presented palmo plantar psoriasis after 46 doses of DAC HYP and received 16 additional doses. Treated with topical steroids; the event did not resolve. For the 38 patients with no prior history of psoriasis, mean number of doses to onset of psoriasis was 24 (median 22, range 3 to 71). Patients received a mean of 11 additional doses (median 3, range 0 to 54). Thirteen patients did not receive any additional dose. Five received systemic corticosteroids and one with PUVA. 21 patients had unresolved events as of December 2015. Of the cases of psoriasis, 8 occurred in patients who also had lymphadenopathy, 3 were associated with thyroid disease (goiter, hyperthyroidism, thyroiditis), one was in a patient with proteinuria, one in a patient with aphthous stomatitis and spondyloarthropathy.

Psoriatic conditions in study 301: 3 patients treated with DAC150 and 1 treated with IFN β 1a developed psoriasis. One of the patients on DAC150 had a prior history of psoriasis. The case on IFN occurred 23 days after the last dose of IFN β 1a and is unlikely related to IFN therapy.

Enteropathy

The wide search used in this analysis identified 45 AE in 36 patients consistent with enteropathy (including PTs of enterocolitis, ulcerative colitis, colitis, enteritis, proctitis, Proctocolitis, colitis microscopic, Crohns disease and inflammatory bowel disease) in the total DAC HYP as of the SUR, which is greater than the 27 cases identified in the previous FDA analysis.

The mean number of doses of DAC HYP before diagnosis in those 36 patients was 24 (median 23, range 1 to 57); and after the diagnoses was 9 (median 3, range 0 to 66). Twelve patients (one third) did not receive any further dose after the event of colitis; 9 received 1 or 2 more doses and the rest received ≥ 3 doses of DAC HYP after the diagnosis of colitis. None of the 36 patients had a prior history of colitis, although 2 had a history of irritable bowel syndrome. As per these datasets, 6 patients underwent colonoscopy, and one underwent an upper GI endoscopy. Of the 36 patients with colitis, 18 received mesalazine or sulfasalazine (oral or per rectum), 14 received systemic oral or IV corticosteroids and 5 received azathioprine. Of the 36 patients with events of colitis, 19 have not recovered as of December 2015.

Of the cases consistent with enteropathy, 5 were in patients who also had lymphadenopathy, one had lymphadenopathy and sialoadenitis, two had aphthous stomatitis, 2 had asthma, and

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the following had one concurrent or subsequent event of polyarteritis nodosa, thrombocytopenia, TSH increased, vasculitis, atypical pneumonia, and one hyperthyroidism and type I diabetes mellitus.

Enteropathy in study 301: Thirteen patients AE consistent with enteropathy, all on DAC150, including the following PTs: colitis, colitis microscopic, colitis ulcerative, enteritis, enterocolitis, inflammatory bowel disease, proctitis and proctocolitis. No such cases were diagnosed in the IFN β 1a group.

In summary, 36 cases of colitis/enteropathy occurred in the total DAC HYP database, including 13 in study 301. No such cases were reported on IFN β 1a in study 301. Colitis can occur at any time, with a mean of 24 doses before diagnosis. No patient had a previous history of colitis. Sixteen of the 36 had other potential immune mediated events. Approximately one third required systemic corticosteroids or azathioprine and approximately half of the patients have not recovered as of December 2015.²⁴

Endocrinopathy

Thyroid disease: 97 patients had potential immune mediated thyroid disease including autoimmune thyroiditis, hypothyroidism, hyperthyroidism, goiter, Basedow's disease, blood TSH increased, blood TSH decreased, thyroxine increased.

Of the 97 patients, 13 had a prior history of thyroid disorder. Of the 82 without a prior history of thyroid disease, mean number of doses before diagnosis was 18 (median 14, range 1 to 60), and the number of doses after diagnosis was 18 (median 12, range 0-73).

Of the 97, 18 had at least one other immune mediated event including 3 patients who had colitis (one associated with Type 1 DM and one associated with lymphadenopathy); 3 in patients who also had a psoriatic rash; 3 in patients with lymphadenopathy, including one who also had thrombocytopenia; 2 in patients with proteinuria; 1 in a patient with alveolitis/idiopathic pulmonary fibrosis; 1 in a patient with vasculitis, 1 in a patient with chronic hepatitis, 1 with sialoadenitis, 1 with splenomegaly, 1 with spondyloarthropathy, 1 with aphthous stomatitis. Two of these patients were treated with systemic corticosteroids (203/901-006 diagnosed with secondary immunodeficit with autoimmune syndrome and 202/765-003; both apparently had a history of autoimmune thyroiditis prior to entering the study.)

Type 1 diabetes mellitus: at least 1 case as of the SUR (in patient mentioned above), plus one after the SUR (with rash, DILI and pancreatitis) and an additional case with rash and pancreatitis. Glucose was not measured in the controlled trials.

²⁴ The 2/18/16 DNP request included the following item, under f) "outcome of immune mediated event" "Be clear as to what the date and relative day for the last dose of DAC HYP (relative the first day on DAC HYP)." The 3/8/16 submission includes the outcome and the date of last dose of DAC HYP, but with a numeric format, not the regular date format therefore it is difficult to know how long these patients have been off-DAC HYP.

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Evaluation of Thyroid disease in study 301

A total of 77 patients (47 on DAC150 and 30 on IFN) had thyroid related events in 301 including the following PTs: autoimmune thyroiditis, Basedow's disease, anti-thyroid antibody positive, blood TSH decreased, blood TSH increased, goiter, hyperthyroidism, hypothyroidism, primary hypothyroidism, thyroiditis, thyroxine decreased, thyroxine increased. Eleven patients had a medical history of thyroid disease prior to entering the study (4 in the DAC150 group, and 7 in the IFNb1a group). Excluding the patients with prior history of thyroid disease, new onset thyroid disease was observed in 43 subjects on DAC150 and 23 on IFNb1a. Of the patients with new onset thyroid disease, 38 did not resolve (23 on DAC150 and 15 on IFNb1a).

Lymphadenopathy

As of the SUR, there are 121 cases of lymphadenopathy/lymphadenitis/lymphoid tissue hyperplasia in the total DAC HYP database. The mean number of doses before diagnosis was 22 (median 19, range 1 to 77) and the mean number of doses after diagnosis was 15 (median 10, range 0 to 60). 15 patients did not receive any further dose after diagnosis, and 13 received 1 or 2 additional doses. Of the 121, 43 are still not resolved as of December 2015.

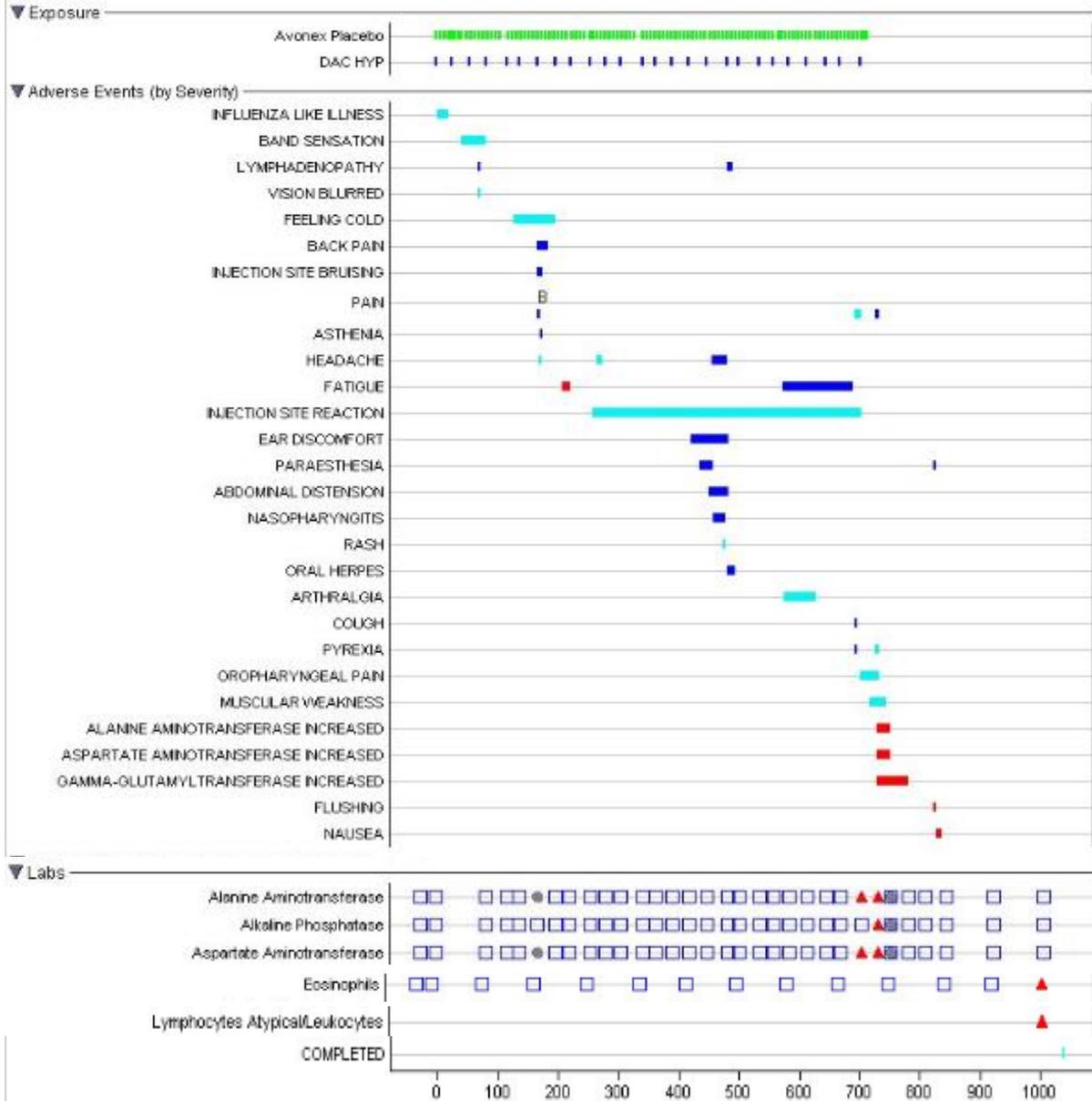
Of the 121 patients with lymphadenopathy/lymphadenitis/lymphoid tissue hyperplasia, 8 had psoriasis; 8 had thyroid disease (hypothyroidism 3, hyperthyroidism 2, goiter 1, autoimmune thyroiditis 1, thyroxine decreased 1); 3 had sialadenitis and 2 had uveitis (one of them also associated with parotid gland enlargement), 4 had enteropathy (1 enterocolitis, one proctocolitis, 1 proctitis, 1 enteritis with sialoadenitis) and one had the following potentially immune mediated events (one each): pancreatitis, atypical pneumonia, scleritis, aphthous stomatitis, proteinuria, platelet count decreased, myositis and autoimmune hepatitis. Cluster mining analyses using Empirica Study identified some patients with more than one potential immune mediated event in study 301, for instance, rash and ALT elevation. Eight patients presented such a combination of AE in the DAC150 group, as compared to only one on IFNb1a. (Patient profiles are presented following this discussion).

In summary, the safety profile of DAC HYP is consistent with CD25/Treg deficiency syndromes described in the literature characterized by rash, enteropathy, endocrinopathy, lymphadenopathy, and other immune mediated reactions (at least 11 cases of autoimmune hepatitis; 4 celiac disease, 3 hemolytic anemia, 4 thrombocytopenia). These reactions may appear at any time during DAC HYP treatment. A substantial number of cases had not resolved after drug discontinuation as of December 2015. A few patients had ≥ 3 of these events, but there were some cases (e.g. rash, DILI, pancreatitis and Type 1 DM).

Selected patient graphic profiles of patients who had immune mediated events are shown below (generated with Empirica Study).

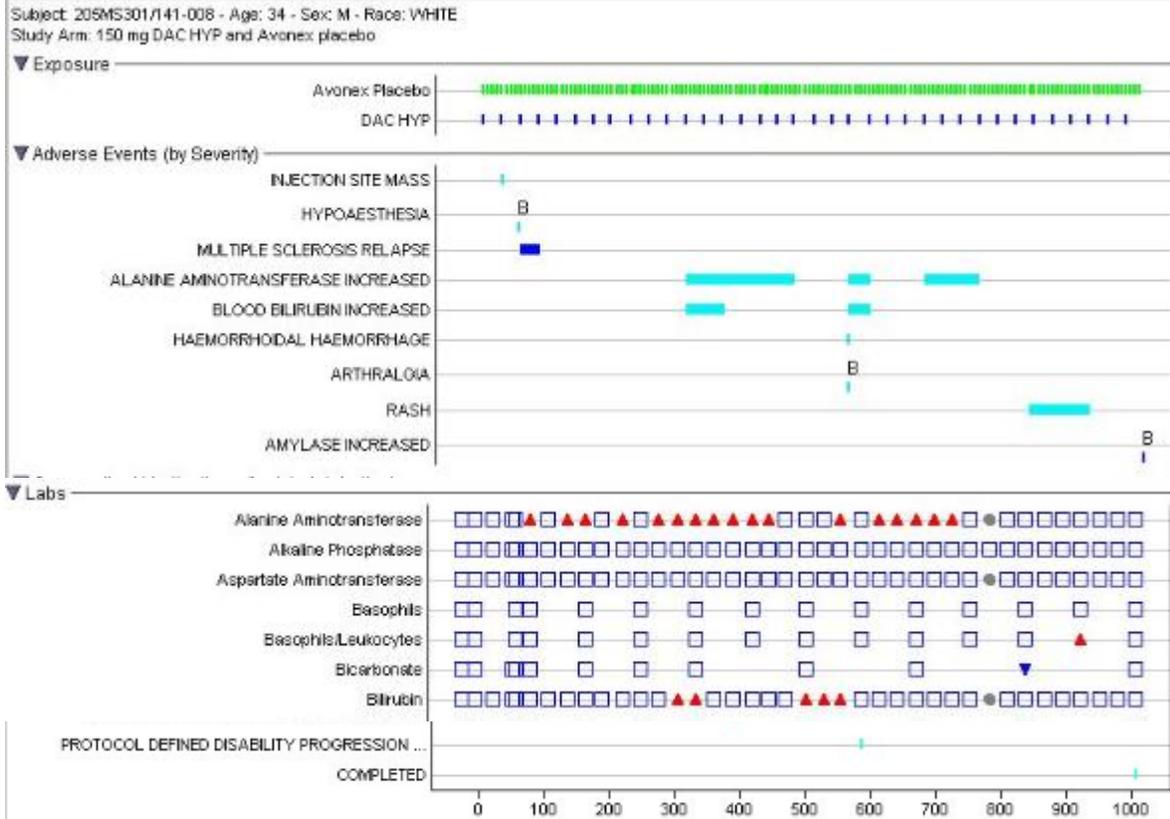
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Subject: 205MS301/110-002 - Age: 53 - Sex: F - Race: WHITE
 Study Arm: 150 mg DAC HYP and Avonex placebo



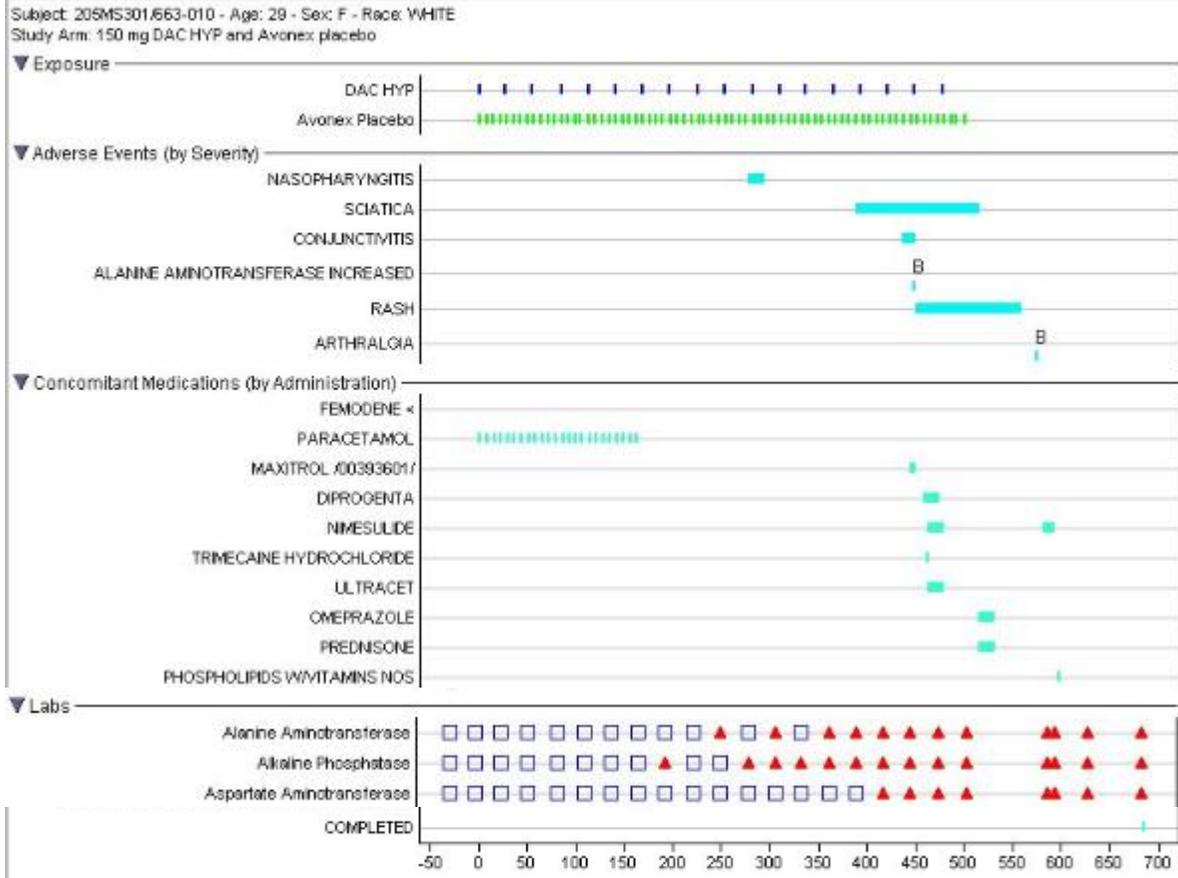
This patient presented lymphadenopathy, fatigue, abdominal distention, rash, arthralgia, cough, fever, muscle weakness, ALT, AST, GGT increased, flushing and nausea. Had prior history of hypothyroidism. Last dose of DAC150 on Day 705. ALT peaked to 500 U/L (normal up to 34) on day 734 of the study (after 26 doses of DAC150). At the time on paracetamol (given for fever and generalized body aches Day 696-733). At end of study also had eosinophilia and atypical lymphocytes.

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This patient had ALT and BR increased, arthralgia, rash and amylase increased but completed treatment.

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This patient had liver enzyme increased, conjunctivitis, rash and arthralgia. Liver enzyme elevation led to drug withdrawal. Event of liver enzyme elevation did not resolve.

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13.3.11 INFECTIONS AND INFESTATIONS SOC, SAE AND AE DROPOUTS

Listing of SAE of pneumonia

USUBJID	Age/ sex	PT	Onset Day	End Day	ACTION taken with drug
Study 201 (both in DAC 300 group)					
454-005	31 F	PNEUMONIA	59	69	DOSE INTERRUPTED
505-018	20 F	TONSILLAR ABSCESS	340	347	NONE
Study 301 (all in DAC 150)					
161-004	53 F	PNEUMONIA	78	80	NONE
162-002	39 F	LOBAR PNEUMONIA	147	153	NONE
441-018	44 F	LUNG INFECTION	339	449	NONE
516-002	41 F	PNEUMONIA	45	55	WD
571-013	22 F	PNEUMONIA	425	435	NONE
624-015	43 F	PNEUMONIA	742	751	NONE
670-008	47 M	PNEUMONIA	109		NONE (NOT RESOLVED)
492-001	39 F	UPPER RESP TRACT INFEC	815	874	NONE
513-003	19 F	CHRONICTONSILITIS	713	714	NONE

SAE in extension and uncontrolled studies are as follows

Study 202		Treatment sequence	PT	Onset	End day	Action Outcome
365-002	40 F	DAC 300/Placebo-DAC 300/DAC 150	BRONCHITIS	629	694	DOSE INTERR
501-019	53 F	Placebo/DAC 300/ DAC 150	BRONCHITIS	68	71	NONE
767-002	27 M	Placebo/DAC 150/ DAC 150	BRONCHITIS	355	365	NONE
450-009	29F	DAC 150/Placebo- DAC 150	TRACHEOBRONCHI TIS	522	523	NONE
505-018	20M	DAC 300/DAC 300	SINUSITIS	557 664	559 648	NONE NONE
Study 203						
353-002	28F	Placebo/DAC 150/	PNEUMONIA	533	554	NONE

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		DAC 150				
505-011	36F	DAC 300/Placebo- DAC 300/DAC 150	BRONCHITIS (also had colitis)	1192	1199	NONE
506-003	45 F	Placebo/DAC 300/ DAC 150	BRONCHITIS	1003	1016	NONE
512-013	53 M	DAC 300/Placebo- DAC 300/DAC 150	PNEUMONIA	1201	1226	DOSE INTERR
502-007	27F	DAC 150/DAC 150/DAC 150	RHINITIS	2151	2153	NONE
506-003	45F	Placebo/DAC 300/ DAC 150	UPPER RESP TRACT INFECTION	459	472	NONE
510-007	46F	DAC 150/DAC 150/DAC 150	TONSILLITIS	1535	1543	NONE
Study 302						
162-107	44 F	DAC 50/Washout- DAC 150	PNEUMONIA	382	394	WD
659-114	34M	DAC 50/Washout- DAC 150	PHARYNGITIS	510	525	NONE
Study 303						
327-005	44 F	DAC 150/DAC 150	PNEUMONIA	1043	1060	NONE
453-048	35 M	DAC 150/DAC 150	PNEUMONIA	692	718	NONE
549-008	31 F	DAC 150/DAC 150	PNEUMONIA	1115	1119	NONE
552-014	47 F	DAC 150/DAC 150	PNEUMONIA	992		WD Not resolved
			PNEUMONIA	991	1038	NONE
571-008	30 F	DAC 150/DAC 150	PNEUMONIA	776	813	NONE
611-049	39 M	DAC 150/DAC 150	ATYPICAL PNEUMONIA	902		WD Not resolved
616-012	36 M	IFNβ1a/DAC 150	PNEUMONIA	49	65	DOSE INTERR
413-002	31F	DAC 150/DAC 150	TONSILLITIS	896	910	DOSE INTERR

Selected narratives from this table:

302/162-107. 44 F. Hospitalized for pneumonia after 8 doses of DAC. She had right side chest pain and cough for 3-4 weeks prior. Meds at time of event included amantadine, aspirin, duloxetine, naproxen, tizanidine and trazodone. Labs showed elevated WBC, anemia (HTC 21%, (normal range 37-47%) with normal platelet count, sodium 134 (normal 137-145 mEq/L) and K of 3.4 (normal 3.5 to 5.1 mEq/L). Chest X-ray showed right middle lobe infiltrate. Serology was negative for Legionella and streptococcus pneumonia. She received a blood transfusion. Treatment included ceftriaxone, cefepime, levofloxacin and vancomycin. She improved and was discharged from the hospital (b) (6) Pneumonia not resolved as of the SUR. (Anemia with 21% hematocrit not reported as AE. No evidence of workup for severe anemia)

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Potential cases of immune mediated lung disease

303/552-014. 47 F, history of chronic gastritis and hypertension. Received 29 doses of DAC HYP in 301. An event of tuberculosis of left lung was reported after 5 doses of DAC in study 303 (34 doses total, last dose given in July 2014, Day 115). She was initially admitted to the hospital from [REDACTED] (b) (6) with dx of community acquired pneumonia and readmitted on [REDACTED] (b) (6) with dyspnea, productive cough, low grade fever. CT of the chest showed bilateral multisegmental pneumonia and lymphadenopathy, raising the possibility of TB. However sputum cultures including PCR of sputum for Mycobacterium TB was negative. She was treated with supportive therapy. A CT in [REDACTED] (b) (6) the diagnosis was “**hypersensitivity pneumonitis past exacerbation phase.**” CT was read as changes “tend to be positive” s compared to the one in [REDACTED] (b) (6). The investigator changed the reporting term to “polysegmental pneumonia.” *This case is probably not TB (she was not treated with antiTB meds). However, it is not pneumonia either. The CT scan was read as hypersensitivity pneumonitis and could be consistent with an immune mediated process, perhaps DAC HYP induced pneumonitis.*

303/301-010. 47 M. Had pneumonia during hospitalization for severe skin rash, on Day 258 to 310 of DAC HYP 150 treatment. He received had placebo in 301. CT scan showed patchy areas of ground glass changes in both lungs, representing **either pneumonitis or a resolving consolidation** following the recent pneumonia. Small lymph nodes were noted in the mediastinum, “likely reactive.” No action was taken with drug because drug had already been discontinued because of rash. Not resolved as of the SUR.

303/ 611-049. SAE Interstitial lung disease/atypical pneumonia. This case was initially diagnosed with “interstitial lung disease (ILD) of unknown etiology.” The investigator later changed the term to atypical pneumonia. The patient, a 42 year old male had received 24 doses of DAC 150 in study 301 and 9 doses in study 303, prior to the event. Last dose was on September 2014. He was hospitalized with chest pain and palpitations and one month history of cough and night sweats. X-rays showed micronodular changes in both lungs, initially thought to be related to congestive heart failure but after negative cardiac workup diagnosed as interstitial lung changes. As per the investigator, this was the third case of interstitial lung disease with daclizumab at this site. The patient received antibiotic treatment at an outpatient clinic and was admitted to a hospital [REDACTED] (b) (6) for workup of abnormal X-rays. A HRCT showed inflammatory micronodular lung lesions, along with mediastinal, hilar and axillary lymphadenopathy. Abdominal US, routine labs and CRP were within normal. Urinalysis showed numerous calcium oxalate crystals and amorphous phosphates. Bronchoscopy and cytological aspirate was negative for infiltrative lesions, neoplastic cells, pathogenic organisms (Mycobacteria, fungi, yeast, pneumocystis). ANA was positive 1:320 granular type; pANCA and cANCA negative. Spirometry was normal. Atypical infection was suspected and a macrolide

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antibiotic was given for 21 days. X-ray improved (b) (6) and **interstitial changes** finally resolved (b) (6) (as per IND safety report from 12 October 2015).

This patient required prolonged hospitalization, bronchoscopy and cytology aspirate that did not show an infection. Patient had a positive ANA. X-rays normalized 9 months after the last dose of DAC HYP. Rather than course of macrolide antibiotic I believe that this could have been an immune mediated event and being off drug is what helped this patient recover.

Listing of SAE of Urinary tract infections

ID	Age/Sex	PT	Onset	End	Comment
Study 201					
109-003	44M	UTI	192	198	Patient had another episode of serious UTI again in study 203, that lasted almost 3 months and led to withdrawal.
Study 202					
765-012	31F	PYELONEPHRITIS CHRONIC	621	729	3 month duration
Study 203					
501-009	44F	UTI	1658	1666	
505-021	39M	UTI	974	983	
Study 301					
128-003	40F	PYELONEPHRITIS ACUTE	557	559	
141-002	50F	UTI	203	204	
162-002	39F	UTI	296	299	
254-012	52F	UTI	63	66	Led to withdrawal.
430-007	42M	UTI	333	346	
600-017	47F	UTI	230	245	
604-012	37F	PYELONEPHRITIS	998	1002	
604-016	53M	UTI	853	859	
622-011	47F	UTI	553	557	
741-001	40 M	UTI	418	423	Presented recurrent UTI on Day 450-456
Study 302					
162-106	46 F	UTI	467	468	UTI by streptococcus pneumonia
Study 303					
311-004	45 F	UTI	314	-	NOT RESOLVED.
412-006	45 M	UTI	132	137	
604-012	37 F	UTI	1040	1044	
747-012	43 F	UTI	143	152	

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Selected narratives are presented below.

203/109-003. Patient had received DAC HYP 150 in studies 201 and 202 (total of 26 doses). After the first dose of DAC in study 203 he had non-serious AE of eczema and psoriasis (July 27, 2012) treated with topical corticosteroids. On (b) (6) had SAE for UTI that required hospitalization and led to drug withdrawal (last dose given in July 2012). Initial treatment included circumcision and antibiotics. Subsequently he had repeated UTIs (E coli; Klebsiella) requiring multiple courses of antibiotics. Event resolved (b) (6) (Day 117 of study 203) almost 3 months after drug was discontinued.

301/254-012, 52 F. UTI. Patient fell down and had a hip fracture on Day 41 after 2 doses of DAC, treated with surgery, antibiotics and non-opioid analgesics. One more dose of DAC was given on Day 58. On Day 63 she was hospitalized with somnolence, vomiting, incoherent speech, delirium, acute kidney failure and hematuria and was diagnosed with a urinary tract infection. She was treated with unspecified treatment. The event of fracture and urinary tract infection resolved on Day 66 and the patient was discharged (“as per the narrative, fully recovered”). DAC was withdrawn. *It appears that this was something more than a simple urinary infection; she may have had been septic, since the patient had acute kidney failure.*

303/311-004 – UTI not resolved as per dataset. 47 year old F, on Day 314 of study 303 presented urinary tract infection after 12 doses of DAC HYP. She received IFN in study 301 with no episodes of UTI. She was hospitalized with right loin and suprapubic pain, fever and altered sensation in the arms, and treated with amoxicillin and gentamicin. As per the narrative the event resolved 2 days later.

SAE suspected to be SEPSIS/SEPTICEMIA OF UNKNOWN ORIGIN (no organism identified)

203/303-005 39 M He had received 26 doses of DAC in 201 and 202, and 16 doses of DAC 150 in 203. Concom meds: lamotrigine, naproxen, allopurinol, enoxaparin, omeprazole. In 201 and 202 transient ALT elevation <2x ULN. Since June 2012 he had inflammatory arthritis with negative ANA and positive RF. ON October 12, 2012 (Day 449 of study 203) ALT 2.4xULN. Total BR normal. Last dose of DAC was given on October 17, 2012. In (b) (6) ALT was 1.4xULN but ALP was 3x ULN. In (b) (6) he had tingling sensation of the skin which developed into a viral skin infection that worsened and he developed a fever and infarct of the fingertips. He was hospitalized (b) (6) with lymphadenopathy, splenomegaly, renal impairment, generalized purpuric rash, hypotension, abnormal clotting suggestive of disseminated intravascular coagulation and microinfarcts of the fingertips. He was diagnosed with **HEMOPHAGIC HISTIOCYTOSIS**. Abnormal labs included high ferritin, low WBC, low Hb, low platelet count, prolonged PT and PTT. Test for Mitochondrial antibody was weak positive and ANCA also positive. Ig titer included IgG >38.2 g/L (ref range up to 16.1), IgA 2.73 g/L (range up to 2.6). CT scan showed enlargement of spleen and liver, extensive bilateral axillary and mediastinal, celiac and para aortic lymphadenopathy, bilateral pleural effusion, ascites, patchy

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consolidation in both lung fields. Differential diagnoses included reactive lymphoid hyperplasia or lymphoma. On [REDACTED] (b) (6), labs showed IgG anticardiolipin antibody positive (93 U/mL).

A lymph node biopsy of 5 lymph nodes from the left axilla could not identify normal lymph node architecture. There was a necrotic area. Within the necrotic area, fibrin thrombi were present within dilated blood vessels. The visible areas of the biopsy specimens were replaced by a polymorphous infiltrate containing large transformed lymphoid cells admixed with small and medium lymphoid cells, plasma cells, and macrophages, which were highly unusual. A lymphoma could not be entirely ruled out.

A bone marrow aspiration and biopsy report stated the sample consisted of hyper cellular bone marrow (approximately 70% to 80% cellularity). Increased numbers of morphologically normal megakaryocytes, mild reactive features, and hyperplasia of the granulocytic series with increased numbers of polymorph neutrophils were observed. The erythroid series appeared normal. The features were those of nonspecific reactive hyperplasia of the bone marrow. On [REDACTED] (b) (6), a supplementary biopsy report stated that the left axillary lymph node appearance would be consistent with a thrombotic microangiopathy with associated nodal necrosis, which was consistent with the clinical diagnosis of antiphospholipid syndrome. Further treatment included chlorhexidine, prednisolone (unclear dose and duration), and enoxaparin. The subject's flank was noted to still have necrosis. On [REDACTED] (b) (6) the investigator confirmed the diagnosis of catastrophic antiphospholipid antibody syndrome associated with septicemia. The event resolved with sequela of skin necrosis.

In [REDACTED] (b) (6) a hematology consultation noted that the subject's auto-antibody profile showed non-specific p-ANCA positivity with a modest titer of 1:80; myeloperoxidase ANCA test was "normal." The overall picture was of a florid reactive immune state triggered by an infection but without any pathogen isolated and with serology that was not suggestive of an underlying connective tissue disorder or a primary anti-phospholipid syndrome. A CT scan of the chest, abdomen, and pelvis on an unknown date [REDACTED] (b) (6) revealed a complete resolution of lymphadenopathy and hepatosplenomegaly.

*Reviewer comment: HPS is a syndrome characterized by **T cell hyperactivation**. There is a primary form that is genetic, and an acquired form, usually secondary to infection or malignancy. Clinical manifestations of HPS overlap with those of sepsis. HPS has been reported in patients receiving immunosuppressors. Because DAC HYP decreases Tregs I believe the event of HPS is plausible related to DAC HYP.*

Subject **301 606-020** 33 year old Male developed **Kawasaki's disease** and multiorgan failure (MOF). Patient had several AE reported after 15 doses of DAC HYP 150. He received DAC treatment from [REDACTED] (b) (6) [Dose #15, Day 393]). Non-SAE of **urticaria and seborrheic dermatitis** were reported Day 414-418, which were preceded by **fever, myalgia and joint pain**. Cutaneous event was described by dermatologist as indeterminate, erythema-edema spots on arms, legs and trunk. An AE of **proteinuria** had been reported after 13 doses,

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from Day 335 to 367. Pharyngitis on Days 417 to 419. On Day 419: hospitalized for SAEs of **bacterial, viral and fungal infection, Kawasaki syndrome and MOF**. Drug was discontinued because of MOF (all other SAE were listed as “no action taken with drug”). Patient was hospitalized on Day 419 with suspicion of **sepsis**. During hospitalization he had WBC of $37 \times 10^9/L$ (normal range 4.0 to 10.0) with 30% band neutrophils and CRP of 91.7 mg/L (normal 0-5.0 mg/L). During hospitalization he also had anemia (reference range 14.0 to 18.0 g/dL), and thrombocytopenia ($67 \times 10^9/L$ (reference range 130×10^9 to 440)), ALT elevation (>5xULN with normal BR), hypercoagulability.

According to an infectious disease consult, the subject had **toxic and allergic erythema**. All blood, bone marrow, CSF and urine cultures were negative. On (b) (6) a bone marrow cytometry revealed a high percentage of activated T cells as well as increased ratio of CD4+ to CD8+ cells (4.3:1). A bone marrow smear showed normally abundant nuclear elements but completely absent erythropoietic and thrombopoietic system. An “imprint specimen” of the lymph nodes revealed an abnormal presentation, with less numerous large and immature lymphoid cells with around 5 nucleoli. Echocardiogram and liver US was normal. Histopathologic examination of lymph nodes revealed partially necrotic changes with indistinct structure. On an unknown date labs showed ANA-, RF- and **myeloperoxidase [MPO] ANCA + antibodies**. The Investigator diagnosed the subject with **systemic vasculitis** in the form of adult Kawasaki’s disease with thrombocytopenia in the course of biological treatment of MS.

ALT elevation was reported Day 477 to 517. Non serious events of generalized erythema, maculopapular eruption, pyrexia and eye infection viral were reported Day 531 to 537; seborrheic dermatitis at elbows and knees was reported on Day 560 (after DAC had been stopped, hence, “no action taken” with drug). Eosinophilia noted on Day 588. The patient completed the study and had his final visit on Day 665. Anti DAC antibody was negative at all measurements.

The patient was treated with various antibiotics, ketoconazole, acyclovir, dopamine, fluids, potassium, platelet transfusion during multiorgan failure as well as several corticosteroids in high doses (dexamethasone, prednisone, methylprednisolone, from Days 414 to 507). Events of systemic vasculitis and multiorgan failure were considered resolved on Day 445. It is unclear what his functional status was after all these events, and whether he was able to discontinue corticosteroid treatment.

Listing of SAE of Infection by specific organisms

201/752-018	52 F	YERSINIA INFECTION (“hepaticyersiniosis”)	After 11 doses of DAC 150. Drug WD.
202/765-003	25 F	KLEBSIELLA INFECTION	After 25 doses of DAC. (in pt with urticaria, thyrotoxicosis leulopenia and chronic

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			hepatitis)
202/501-013	35 F	C. DIFFICILE COLITIS	After 56 doses of DAC.
301/600-018	52 F	NEUROBORRELIOSIS	After 35 doses of DAC
301/610-009	42 F	LYME DISEASE	After 20 doses of DAC
303/453-048	35 M	BRUCELLOSIS	After 25 doses of DAC. DRUG WD
303/622-016	50 M	C. DIFFICILE COLITIS	After 35 doses of DAC.
303/ 645-006	30 M	SALMONELLOSIS	After 45 doses of DAC

Selected narratives are shown below.

201/752-018. Yersinia infection. "Hepatitis form of Yersiniosis"

52 year old F from Russia presented "Yersinia infection" after 11 doses of DAC HYP 300. No relevant meds were listed. After the 10th dose and between weeks 36 and 40, the patient presented a toxic skin eruption of moderate severity. Drug was interrupted but resumed. After the 11th dose drug was withdrawn because of skin eruption. She was treated with topical betamethasone, antibiotics and antifungal meds. The last dose was given on Jan 11, 2010. On March 5, 2010, two months after the last DAC dose (Day 339 of study), patient was diagnosed with Yersinia infection (mild). On 03 March 2010, laboratory results revealed LDH (lactate dehydrogenase) 521 U/L (reference range: 53 to 234 U/L), ALT (alanine transaminase), 975 U/L (reference range: 6 to 34 U/L), and AST (aspartate transaminase) 1091 U/L (reference range: 9 to 34 U/L). **On 10 March 2010, ALT was 1538 U/L (reference range 0-41 U/L) and AST was 1174 U/L (reference range 0-38 U/L).** On March 16, 2010, IFA test of HBS (Indirect Fluorescent Antibody test of anti-hepatitis virus B surface antigen) was positive and the infection was deemed a serious adverse event. Lab results on 31 March 2010 showed a decrease in ALT (159 U/L) and AST (123 U/L), and LDH was within the normal range. As per the narrative the diagnosis was changed from hepatitis B to Yersinia infection. "The event was confirmed as yersinia infection and subject was treated with Rovigon and ursodeoxycholic acid from 05 March to 31 March 2011. The event was considered resolved on 31 March 2010." The investigator considered the event of LFT elevation and Yersinia infection as not related to drug. Liver enzyme elevation was not captured as an AE in the CRF.

ALT/AST normal up to Week 48 (Day 337) when ALT was close to 20xULN, AST 32xULN with mild elevation of ALK P, Total BR 1.1xULN. By next available study measurement (Day 365) ALT/AST <5x ULN. Resolved by Day 421. Anti-DAC ab negative. Neither narrative nor patient profiles include autoantibody panel and infection panels. As per the narrative, ALT peaked on March 10 (around Day 344) to 1538 U/L (37x ULN). BR was not provided. THE IFA tests is said to be positive for Hepatitis B. In response to an FDA request for information supporting the diagnosis of yersiniosis and whether there was any liver autoantibody workup. A response submitted on 9/2/15 did not add substantial information to support the diagnosis of yersiniosis. The event was considered resolved on 31 March 2010. More than a year later, on 18 May 2011, the event term was changed to "hepatitis form of yersiniosis." No autoimmune disease serologies were

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reported. DAC HYP had been discontinued after 11 doses (Day 286).

The case did not have adequate work up. Patient improved apparently without hospitalization and without steroid treatment after approximately 4 months off drug. Poor quality data collection. **In my opinion this case is consistent with DILI or perhaps Hepatitis B.**

Patient **303/453-048 – PYREXIA.** had a very complex clinical picture. He developed pneumonia after 25 doses of DAC150 (first and last dose in study 303, study Day 692) that resolved, but he was re-hospitalized because of persistent fever, arthralgia, hepatosplenomegaly pulmonary consolidation and pancytopenia on Day 713 of DAC exposure. At that time a diagnosis of brucellosis was made. Labs showed pancytopenia, and mild ALT elevation along with increased LDH and ferritin. He had a positive ANA 1:80. An abdominal US showed splenomegaly without abdominal lymphadenopathy. An axillary lymph node was biopsied for suspected lymphoma. Bx showed follicular architecture with atypical proliferation and moderate number of mitosis with some large nucleated cells with an “activated” appearance. Fine needle aspiration of bone marrow was normal. Biopsy findings included microscopic description of the lymph node with altered architecture due to the presence of extensive aggregations of histiocytic elements. The lymphoid population consisted of elements of variable size, with some large nucleated cells having an activated appearance. The limited number of white sections received did not allow a complete definition of the phenotypic profile of the lymphoid population. The patient improved after treatment with clarithromycin, levofloxacin, rifampin and minocycline. He was also treated with prednisone 5 mg day (for “erythema”). Patient was discharged (b) (6) with diagnosis of **brucellosis with secondary hepatitis**, MS and pneumonia, and disc. On June 3, 2014 the investigator amended the term of “suspected lymphoma” to “suspected infection” which was considered related to study drug. Daclizumab was permanently discontinued.

Reviewer comment: As per additional information submitted on July 30, 2015 in response to an FDA request, the diagnosis of brucellosis was based on a reportedly positive IgM serology for Brucella. “The subject is from Catania, Italy, where brucellosis is endemic.”

301/600-018. 52 F, diagnosed with **neuroborreliosis** after 20 doses of DAC HYP 150. It was considered of mild intensity and considered resolved after 6 days. No action was taken with DAC HYP. A diagnosis of “asymptomatic borreliosis” was done in June 6 2013 and she was treated with doxycycline. On (b) (6) she was hospitalized for observation of neuroborreliosis. At the time she had spastic paresis of the four limbs and also had a urinary tract infection. Because of a systolic murmur she had an echocardiogram that showed calcification of the aortic valve cusp, with moderate regurgitation with hypertrophy of the interventricular septum and impaired relaxation of the left ventricle. CSF showed negative Anti-B burgdorferi IgG and IgM antibodies in the CSF. The patient continued treatment and completed the study. *The sponsor commented that the subject had no clinical or lab findings of CNS Lyme Disease, but the investigator did not change the event term. I am not sure what this*

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event was. In my opinion perhaps this was MS relapse or MS pseudo exacerbation because of the urinary infection.

301/610-009 42 F dx with **Lyme disease** after 20 doses of DAC HYP 150. Considered “mild”. No action was taken with the drug. A non SAE of erythema on right calf was reported on Day 22, and was preceded by a tick bite. Concomitant meds before the event were piracetam and vinpocetine. She was treated with ceftriaxone, paracetamol and amoxicillin. Subsequently, this was considered the initial manifestation of Lyme disease. On Day 35 a SAE of Lyme disease was reported (erythema migrans). In addition to IV ceftriaxone, amoxicillin and paracetamol she was treated with iron, amitriptyline, hydrocortisone and loratadine. She had positive IgG and IgM ab serology. The initial erythema resolved by Day 47; the event of Lyme disease resolved on Day 578. Additionally, a no serious event of lymphadenopathy was reported on Day 512 after 19 doses of DAC HYP. The investigator considered the event mild and not related to study treatment but drug was discontinued as a result of the event, which was considered unresolved. However, a SAE of lymphadenopathy was reported on Day 574, of moderate severity. “No action was taken” with drug, because it had already been discontinued because of non-serious lymphadenopathy. On (b) (6) (Day 567) and she was hospitalized for lymphadenopathy (in nuchal region, axilla and groin) and rash (skin lesion on the face, neck, trunk, arms hands and anterior surface of lower legs). This occurred 17 months after the diagnosis of erythema migrans. Enlarged peripheral lymph nodes had been present since (b) (6). A computed tomography scan of the chest (b) (6) showed enlargement of the mediastinal lymph nodes. An ultrasound suggested inflammatory lymph nodes. Serology showed negative autoantibodies (ANA, ANCA, AMA, RF) and evidence of recent Lyme disease (High IgG, IgM still mildly elevated). As per the narrative “A dermatology consultation on an unknown date noted polymorphic lesions, **in part related to a generalized drug-induced skin reaction, partly erythema multiforme, and partly seborrheic dermatitis.** A pulmonary consultation on an unknown date noted generalized enlargement of lymph nodes after interferon therapy for MS (lymph nodes of the neck, axilla, groin, and mediastinum), which was probably of the same etiology.” A biopsy of the axillary lymph node showed “lymphatic node pattern”.

This is a complex case in which there is serologic evidence of recent Lyme disease infection, although the initial diagnosis of erythema migrans was 17 months earlier. In my opinion the rash and lymphadenopathy may be related to daclizumab, but are confounded by underlying Lyme disease. The biopsy was not helpful at all.

C Difficile infections

There were two cases of C Difficile infection (203/501-013 and 303/622-016) on HYP 150.

203/501-013 37 F diagnosed with C Difficile colitis on Day 452, after 30 doses of DAC HYP 150. On (b) (6) (Study Day 452), the subject was hospitalized due to 5-day post-antibiotic (amoxicillin) diarrhea of up to 20 stools per day. Laboratory results revealed elevated CRP,

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hypokalemia, and the presence of *Clostridium difficile* toxin B; urinary tract infection was diagnosed. Treatment included diet, hydrating infusions, metronidazole, electrolyte supplementation, and ofloxacin for urinary tract infection. There was gradual improvement and disappearance of diarrhea, allowing the diet to be broadened. Patient was discharged home 6 days later in good general condition, and the event of urinary infection and *Clostridium difficile* colitis resolved. However, subsequently the patient had recurrent diarrhea. On Day 482 she was hospitalized with dx of mild enteritis and chronic diarrhea. Stool culture **and C diff A and B toxin were negative**. Treatment included prednisone, metamizole, mesalazine, saline, glucose, hydroxyzine, potassium and ciprofloxacin. “Clinical improvement and decrease of stool frequency to 3-4 times a day without blood were achieved”. This implies that there was bloody diarrhea at some point. The event of diarrhea resolved 9 days after admission and pt was discharged. At the time of last follow up the event of enteritis was ongoing. DAC HYP was interrupted (b) (6) but restarted in April 2013. .

*C diff infection occurred after amoxicillin treatment for urinary infection. The infection resolved, but she had persistent enteritis that required treatment with prednisone and mesalazine. Event was ongoing at the time of last follow up. Rather than C difficile this appears to be **non-infectious colitis**. A recent report in the literature discusses a case in which an initial diagnosis of c. difficile infection was later diagnosed as ipilimumab-associated colitis. The literature case was successfully managed with fluid resuscitation and steroids. I believe that patient 203/501-013 may have DAC HYP- induced immune mediated colitis. It is important to know what happened after re-starting DAC HYP. In response to a request for clarification, on 3/3/16, the applicant provided no support for a diagnosis of C diff infection. Moreover, the patient did have a nonSAE of seborrheic dermatitis and ALT elevation, making the case consistent with an **IPEX-like syndrome**. **The short narrative included in the response does not state whether DAC was discontinued or not.***

303/622-016 –“*C difficile infection*”. 52 year old M received 27 doses of DAC 150 in study 301 and 7 doses in 303 before the onset of the diagnosis of C Diff infection. He had a prior history of Chron’s disease (17 years prior to entry). The patient was hospitalized with a SAE of acute bloody diarrhea (exacerbation of Chron’s disease) on Day 193 of study 303. He was treated with loperamide, prednisone acetate, electrolyte solutions and saline, mesalazine and sulfasalazine. C Diff Toxins A and B in stool were negative. Diarrhea resolved on Day 200. Treatment with DAC HYP was continued. On Day 224 a SAE of “inflammation of small intestine and large intestine due to C difficile” was reported (after 8 doses of DAC.) In addition to prednisone, mesalazine and sulfasalazine he was treated with vancomycin, antidiarrheal microorganisms and rifaximin. The event was considered resolved on Day 235. (b) (6) the subject was hospitalized on an emergency basis with 2-month history of abdominal pain with accompanying frequent bloody diarrhea (up to 10 times per day), weight loss, and progressing weakness. The narrative states that Medical history included non-treated ulcerative colitis (*versus prior dx of Crohn’s in other part of the narrative*). An endoscopic examination of the inferior segment of the gastrointestinal tract revealed endoscopic image of ulcerative colitis, which was confirmed

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in the histopathology test. *The narrative states that a stool test was reported to be positive for C difficile but does not specify which test or when.* On (b) (6) the subject was discharged from the hospital in a satisfactory general condition. At the time of reporting, the subject's most recent dose of study treatment was on (b) (6) (Day 204). Additional information on the status of the subject's participation in the study (i.e., ongoing, completed, or withdrawn) was not available at the time of reporting.

As many narratives, this one is confusing in terms of which medications the patient was taking at the time of onset of the event. The initial part of the narrative uses relative days on study, while the "supplemental information" uses actual dates. The narrative mentions a prior diagnosis of Chron's disease and that at the time of the event of acute diarrhea the patient was taking sulfasalazine and mesalazine. The supplemental information states that there was a history of ulcerative colitis that was not treated. It is unclear whether DAC HYP was discontinued or not. The outcome is unknown. This conflicting information points to the bad quality of this submission. Request for clarification and follow up is needed. As per information submitted on 3/3/16, this patient had positive stool for C diff bacilli, toxin A and B and GDH antigen. The event resolved on Nov 7, 2014, and he withdrew consent on August 27, 2015 because the drug was ineffective.

These two SAE of C. difficile infection presented with colitis and negative C. diff toxin A and B in stool. A recent report in the literature discusses a patient referred for possible fecal microbiota transplantation for refractory diarrhea secondary to c. difficile infection. This patient was later diagnosed as ipilimumab-associated colitis. The literature case was successfully managed with fluid resuscitation and steroids. I believe that patients 203/501-013 and 303/622-016 may have DAC HYP- induced immune mediated colitis.

SAE of mycobacterial infections

301/611-009. 34 M from Poland, On Day 334 presented non serious AE of **maculopapular rash** on face and hands after 13 doses of DAC HYP. Concomitant meds were fenofibrate, paroxetine and rosuvastatin. Rash was treated with topical corticosteroids and antibiotics. The event resolved by Day 394. On (b) (6) (Day 414) an AE of pulmonary tuberculosis was reported, after 15 doses of DAC HYP, leading to drug discontinuation. Patient was hospitalized. A CT of the chest showed multiple nodular tissue changes in both lungs ranging in size from 12 to 40 mm, with pleural thickening and **hilar lymphadenopathy**. Abnormal labs included WBC of $11.9 \times 10^9/L$ (nl up to $10 \times 10^9/L$) and low lymphocyte count (15.7%; normal 20-45%), and elevated CRP. On a subsequent admission he underwent bronchoscopy and CT guided transthoracic needle biopsy that was non-diagnostic. On a third hospitalization he underwent open lung biopsy of a right lung nodule that showed nodules consisting of thrombotic necrosis surrounded by granulation tissue consisting of epithelial histiocytes and giant multinucleated cells most probably **in favor of tuberculosis**. Lack of apical involvement is more consistent with primary TB (vs. reactivation). TB was reported as resolved on an unknown date (b) (6)

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202/303-006 42 F from the United Kingdom. Mycobacterium abscessus diagnosed on Day 346, after 11 doses of DAC HYP. She received placebo in 201 and DAC HYP 150 in study 202. Hx of hypothyroidism. Meds at time of the event included amoxicillin clavulanic for UTI prophylaxis, levothyroxine and baclofen. On an unknown day in May 2011 she returned from a recent trip to Pakistan with pleuritic chest pain, productive cough and weight loss. A sputum sample was positive for acid fast bacilli that was later identified as mycobacterium abscessus. The clinical significance of this finding was unclear; it was thought to be “a contaminant.” She had normal WBC and was not lymphopenic. Later (b) (6) she developed hemoptysis. HRCT showed inflammatory nodules in the anterior segment of the right lower lobe. She was admitted to the hospital for further workup but discharged after a few days without specific treatment given for the lung infection. A follow up mycobacterial culture was negative. She had bronchoscopy and bronchial washing that showed “coliforms.” Lung infection was treated with ciprofloxacin for non-specific bacterial infection. No further doses of DAC were given. The event was considered resolved in September 2015.

This was not a mycobacterium tuberculosis infection. Mycobacterium abscessus may have been an incidental finding in a patient with bacterial pneumonia.

A case of “Probable tuberculosis” was reported as 15 day report (Not in ISS):

303/747-005* Pneumonia. Reported as 15-day report (2015BI067097.) “ A 49 year-old female from India received 36 doses of DAC HYP 150 in 301 and 12 doses in 303. She was hospitalized for persistent fever, severe cough at night with expectoration and shortness of breath on exertion after approximately 1 year of treatment with Daclizumab HYP in the extension study. Subject underwent extensive diagnostic testing which was negative for tuberculosis. The chest x-ray was considered normal. Initial contrast enhanced computed tomography (CECT) of the chest showed multiple randomly distributed nodules of varying sizes scattered through bilateral lung parenchyma. Later on, additional CECT showed hepatomegaly and patchy consolidation in the left lower lung lobe with two nodules in both lower lung lobes. Histopathology report of bronchoscopic biopsy showed granulomatous inflammation. Antituberculosis treatment was started as pulmonary tuberculosis was suspected despite negative testing. The study drug was permanently discontinued. The differential diagnosis included fungal infection (positive aspergillus galactomann test). Laboratory results showed anemia, leukocytosis and prolonged PT/PTT (Hb% 8.50 gm/dl (reference range 12 – 15), total leukocyte count 17500/mm³ (reference range 4000-10000), prothrombin time (PT) 15.50 sec (reference range 10-13), INR 1.40, and activated partial thromboplastin time APTT 35.50 sec (reference range 22-32). Liver enzymes and renal function test (RFT) were reported as normal. Blood culture was negative; cytopathology report from BAL was negative for malignancy. A bone marrow aspiration gram staining showed scanty number of polymorphs with mild plasmocytosis and no organisms in the gram’s smear of the specimen. On (b) (6) laboratory showed leukocytosis, hyponatremia, low total protein and low albumin (TLC 22800/mm³, sodium 121 mmol/L (reference range 135-145) potassium 4.70 mmol/L (reference range 3.5-5.0) chloride 81 mmol/L (reference range 96-106), alkaline phosphatase 160 U/L (reference range adult <130), normal bilirubin, total

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proteins 5.60 g/dl (reference range 6.0-7.5), and albumin 1.80 g/dl (reference range 3.0-5.0).

She was treated with wide spectrum antibiotics and antiTB therapy, antifungal and antiviral drugs, as well as iron, folate, albumin, packed red blood cells, vitamins, acetaminophen, diclofenac and bromocriptine. She was discharged (b) (6), on anti TB medication. The final diagnosis was pulmonary tuberculosis. The event is ongoing.

*Reviewer Comment: The patient had lung nodules and hilar adenopathy along hepatomegaly, anemia, hyponatremia, hypokalemia, low albumin. She underwent bronchoscopic lung biopsy and bone marrow biopsy. Cultures were negative but she was treated empirically with antituberculous, antibiotic, antiviral and antifungal medications. Daclizumab was discontinued. As per follow up information submitted on 3/3/16, the subject was not treated with bromocriptine, but instead with Bromorex (bromhexine) for cough. Culture report findings of July 2015 (from a bronchial wash specimen taken on 27 May 2015) reported that a smear of the specimen was negative for acid fast bacilli, and that **culture was positive** showing growth of mycobacteria sps and growth of **M. tuberculosis complex** after 6 weeks of incubation. The drug sensitivity test by line probe assay indicated sensitivity to isoniazid and rifampicin; resistant to NIL. At the time of the investigator's report, the subject's condition was improving. As of 20 Feb 2016, the event of pulmonary TB is ongoing.*

SAE VIRAL INFECTIONS

Viral infections HLGT in Total DAC HYP

Study 201		
110-005	18 F	VIRAL INFECTION and CMV infection after 13 doses
763-005	24 F	CHRONIC HEPATITIS B after 9 doses
Study 301		
161-004	53 F	VIRAL INFECTION after 47 doses
254-003	23 M	INFLUENZA after 45 doses
606-020	33 M	VIRAL INFECTION after 15 doses
610-003	27 M	MENINGITIS VIRAL after 47 doses
678-008	19 M	HEPATITIS A after 47 doses
741-004	29 F	VARICELLA after 40 doses
742-005	47 F	DENGUE FEVER after 39 doses
Study 202		
500-009	53 F	INFECTIOUS MONONUCLEOSIS after 21 doses
Study 203		
453-016	35 F	HERPES ZOSTER (Facial) Event occurred after 79 doses of DAC. This patient received DAC 300 in 201 and part of 202, and DAC 150 in 203
506-012	45 F	HEPATITIS C after 31 doses of DAC had elevated glucose and glucosuria and mild thrombocytopenia in study 202; developed ulcerative colitis in study 203. She was later diagnosed with Hepatitis C based on

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		positive Hep C RNA. (Patient was described under GI system disorders). <i>Unclear if de novo or reactivation.</i>
508-013	39 M	INFECTIOUS MONONUCLEOSIS after 53 doses of DAC
565-003*	29 M	15-day IND safety report. HERPESZOSTER in the trigeminal area after unknown number of doses. Treatment started in July 2012. Last dose before the event was April 2015. Lesions were reported as very deep and necrotic with surrounding erythema and edema. Right lower eyelid was swollen but cornea was normal. Treated with acyclovir and ganciclovir eye ointment. The event resolved with scars by June 2015. At that time he had bilateral eczematous papules and erythematous plaques on both forearms, which was treated with topical treatment. Study drug was not re-started. By August 2015 the lesions had improved but not completely disappeared.

Source: MO analysis, JMP, ADAE3 SUR. All patients received DAC HYP 150 in the base and extension study unless noted otherwise. An additional cases of acute viral Hepatitis C was reported as an IND safety report after the cutoff of the SUR.

Extended narratives of selected cases from this table are presented below

Cases of Viral Hepatitis

201/763-005 **Chronic Hepatitis B.** 24 F. At week 28, 8th dose, ALT was elevated. She received one more dose (week 32). She was diagnosed with “**chronic hepatitis B with the minimum degree of activity**” considered serious and not related, based on a positive HB SAg and HB core antigen positive. She was hospitalized and treated with insulin, vitamins and IV fluids. Drug was discontinued. On day 171 ALT was 5x ULN with normal BR. ALT peaked to 18xULN on Day 203, with total BR almost 3xULN and elevated ALP. At early termination (Day 240) ALT was still 4x ULN, total BR was 1.4 and ALP was 123 U/L. *It appears to be a case of **Hep B viral reactivation.** Event was not resolved at last FU.*

303 554-022* **DILI and Hepatitis C reactivation.** IND safety report (2015BI124488, (b) (6)). 28 year old female. On August 22, 2015, after 47 doses of DAC HYP felt nausea and had fever 38C following a urinary tract infection treated with amoxicillin. On (b) (6) she was noted to have icterus and dark urine. ALT was 1785 u/l (nl 10-47), AST was 838 (nl up to 38) and total BR was 9.9 (nl up to 1.6). She was hospitalized with suspicion of toxic hepatitis versus viral hepatitis. DAC HYP was discontinued. EIA diagnostic testing of viral hepatitis **anti HCV and core HCV tested positive.** She was treated with prednisolone. Use of antiviral treatment (recombinant INF) was planned. At the time of discharge, liver enzymes were still elevated. 28 year old female. On August 22, 2015, after 47 doses of DAC HYP felt nausea and had fever 38C following a urinary tract infection treated with amoxicillin (August 20-22). On (b) (6) she was noted to have icterus and dark urine. ALT was 1785 u/l (nl 10-47), AST was 838 (nl up to 38) and total BR was 9.9 (nl up to 1.6). She was hospitalized with suspicion of toxic hepatitis versus viral hepatitis. DAC HYP was discontinued. EIA diagnostic testing of viral hepatitis **anti HCV and core HCV tested positive.** She was treated with prednisolone. Use of antiviral treatment (recombinant INF) was planned. At time of fu safety report, the event of acute viral hepatitis C

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was ongoing. On (b) (6) fibroelastometry of the liver was performed and elasticity of the liver was assessed and found to have **Fibrosis F III stage**. The patient had no hx of drug abuse but the risk factor for hepatitis C was a tattoo. ALT were down to normal by October 2016. On a fu report (Jan 25, 2016) the investigator amended the diagnoses to to amoxicillin-induced liver injury and chronic viral hepatitis C, low viremia. She was started on interferon treatment.

In my opinion this is a case of acute reactivation of chronic hepatitis C. In my opinion this is related to DAC HYP's immunosuppression.

These cases appear to be de novo hepatitis C, not directly related to DAC HYP but it is important to see the course of the disease and how long they take to recover.

There are two SAE of **infectious mononucleosis**, none of which are consistent with acute mononucleosis, as described below.

202/500-009. 53 F. Infectious mononucleosis was diagnosed Day 285 to 291 of study 202. Patient completed study 202 but did not enter 203. It is unclear how the diagnosis of infectious mononucleosis was made at the time of mild ALT elevation. No lab evaluation in patient profile supports such diagnosis. The narrative states that “(b) (6) the subject was hospitalized for infectious mononucleosis. Laboratory tests revealed the presence of Epstein-Barr virus and IgG antibodies; IgM was negative.” *I am not convinced of the diagnosis of acute infectious mononucleosis. Perhaps it was a reactivation.*

203/ 508-013 41 M. On Day 740 of study 203 diagnosed with infectious mononucleosis, which eventually became serious and led to drug withdrawal. Last dose of DAC was on (b) (6) (Day 757 of study 203). The event was characterized by high fever with stomatitis and erythema of the throat. As per the narrative, “test for mononucleosis was positive”. US showed that the liver was somewhat enlarged. The patient had mild increase in ALT up to 1.5xULN with normal AST, BR and ALP throughout study 201 and 202. ALT increased on Day 785 (12xULN) along with AST 7xULN, with normal BR and ALP but elevated LDH. No further doses were given. WBC was unremarkable during the study. Resolved by Day 810 of study 203. As per the patient profile, on 4/12/13 (Day 810), ANA negative, AMA negative, **Anti-Smooth muscle ab positive 1:160**. EBV EBNA antibody consistent with past infection. EBV VCA IgG positive, IgM negative. *Lab data does not support a diagnosis of acute infectious mononucleosis. Moreover, there is a positive ASMA titer which is characteristic of autoimmune hepatitis. Last dose of DAC was (b) (6) peak ALT was on 3/18/13, and event resolved by 4/12/13. I would not say that this is AIH because the event resolved quickly without corticosteroid treatment. Perhaps this is EBV reactivation or it may be DILI.*

201/110-005 18 F. CMV Infection. CMV hepatitis. The patient had several nonserious events during 201 including a rash (diagnosed as tinea versicolor), headache, nausea, dyspepsia, vomiting, recurrent viral infection, gastritis, urinary tract infection, MS relapse. A SAE of Viral fever (“pyrexia”) and gastritis was reported on Days 76 to 80. At that time she was hospitalized for about a week. On (b) (6) (Day 375), approximately one month after the last dose of

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DAC (which had been on Marc 29, 2011) the subject was hospitalized for observation for **acute hepatitis**. She was vomiting, had dark urine and elevated liver enzymes, diagnosed as CMV infection (Day 375 to 480). She also had fever (Day 388 to 392-451 and -452, 469-473), mouth ulcers (day 405 to 409), weight decreased, face swelling (Day 456-463), pleuritic chest pain (Day 469-473) and peripheral edema (Day 456-463). As per the narrative, on an unknown date in (b) (6) CMV IgM and IgG serologies were both positive. On (b) (6) serum polymerase chain reaction (PCR) was negative for CMV. On an unknown date, fine needle aspiration cytology (FNAC) of a lymph node showed “reactive population of lymphoid cells composed of small mature lymphocytes, large lymphocytes, plasma cells, and macrophages. Numerous crushing artifacts were seen. No granulomas/giant cells were seen. Findings were consistent with reactive lymphadenitis.” Hepatitis tests were negative. CT of chest and abdomen were normal. In (b) (6) total protein was normal, with **low albumin** (24%, normal 60-72%) and high Gamma globulin (62%, normal 8-15.8%). IgE was also elevated (1647 IU/ml, normal up to 165). Hepatitis B, C and E testing was negative, but a **CMV test from July 8, 2011 tested positive for CMV DNA** (low level, <2.6 log copies/ml). The patient was readmitted on (b) (6) for anorexia and elevated liver enzymes. She received IV prednisolone for 4 days (narrative states that reason was not recorded). She had a **LIVER BIOPSY** that showed “fibrous expansions with occasional portal to portal bridging. The portal tracts showed marked infiltrations by lymphocytes and plasma cells with marked interface hepatitis. Focal (spotty) lytic necrosis, apoptosis, and inflammations were observed. One to four foci per 10x objective were observed. No cytomegalovirus inclusions or granuloma were seen in the examined sections, however, stains for CMV antigen showed scattered **Kupffer cells lining the sinusoids and few inflammatory cells showed viral antigen to Cytomegalovirus (CMV) as particulate staining of the cytoplasm**. Further examination of the liver biopsy showed a periportal inflammation with lymphomononuclear cells spilling into adjacent lobule. Several hepatocytes showed feathery degeneration, and occasional hepatocytes appeared enlarged with prominent nucleoli. No cholestasis, necrosis or fibrosis was noted.” The biopsy report stated that the features were “suggestive of CMV hepatitis.”

CMV infection was treated with ganciclovir Day 452 to 479, multivitamins, IV fluids, URSO, ondansetron. She was also treated with gabapentin “for CMV infection” and chloroquine phosphate for fever (“anti-malarial”). Lab evaluation in patient profile shows anemia (at screening was normal low, but starting on Day 169 Hb level was below normal); intermittent WBC below normal since Day 86. Liver enzymes were normal on Day 280. On Day 308 ALT was 5xULN with AST 4xULN. **Peak ALT was almost 12xULN with AST 14xULN** on Day 370. BR was slightly elevated. After an initial improvement, ALT and AST increased again up to 10 and **14x ULN respectively on Day 430**. BR was 1.5xULN on Day 430. ALT normalized completely and AST was 1.5 ULN on Day 464. Urinalysis showed intermittent trace protein during the study. Leuk esterase and urine nitrate were positive only once, suggesting that the trace protein *could have been* caused by other than a urinary infection. During the study she dropped from 45 kg to 32 kg (13 kg, **almost 25% of her weight**). As per the narrative, hematology, chemistry, urine tests from August 2011 were reportedly normal, and the event of CMV infection was considered resolved on August 20, 2011. As per the patient profile, there were follow up visits up to week

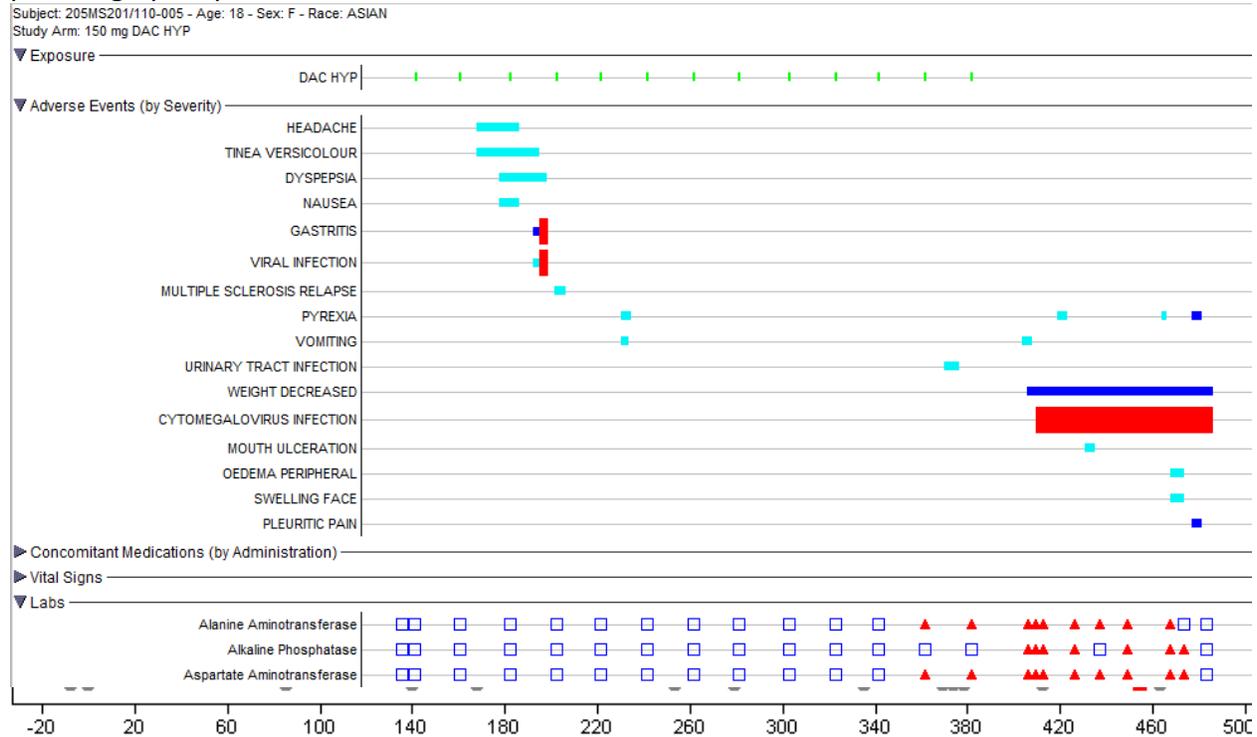
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68 (August 4, 2011, Day 478) but then the patient was **lost to follow up**. The Empirica Study patient graphic profile is below.



The last dose of DAC was on Day 336. Event of CMV infection was reported as starting on Day 375 and resolved on Day 480 (almost five months after the last dose) after showing up and downs in liver enzymes. *It would have been desirable that this patient had a longer follow up, because there are at least 3 peaks on ALT/AST increase, and it is not known whether she may have had further ALT elevations after Day 480.*

202/363 008 - ASEPTIC MENINGITIS

27 M. He received 13 doses of DAC 150 in 201. Hx of food and pollen allergies. During 201 patient had episode of rash, body tinea, gastrointestinal infection, seborrheic dermatitis (periocular eczema) and MS relapse. Treated with cetirizine, ciclopirox, emollients. Methylprednisolone Day 307 to 310. Last dose of DAC (#13) was on Day 340. He entered placebo treatment in study 202. Had Intermittent diarrhea, Day 374 of study 201 = Day 6 of study 202, more than 1 month after the last dose of DAC. Fever on Day 21-32 of study 202. Vomiting, neck pain; **Drug withdrawn Day 407 because of ASEPTIC MENINGITIS** (reported on Day 39 to 52 of study 202). **Maculopapular rash reported on Day 403** to 410 (Day 35-42 of 202). "No action taken" because was already discontinued. An event of wound at site of skin biopsy was reported On Day 409 (Day 41-51 of 202). Meningitis resolved on Day 420. Decreased visual acuity of the right eye was reported at the end of study visit, 4 months after the event of meningitis. Acyclovir was given empirically (2.25g IV Day 39 to 46 of study 202) along with ampicillin (6g PO Day 39 to 52) and ceftriaxone (2g IV Day 39 to 52). Labs: Week 8

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(Day 58 of study 202: WBC 11.86; Eos 0.64, neutrophils 8.34; ALT 69 (1.6xULN). Other labs normal. Anti-DACAB in 201: screen negative; **at week 24 (Day 169) positive; neutralizing ab also positive**. Week 52: negative. In study 202 Anti DAC antibodies were positive at week 8 (Day 58: 46.6, no units); week 20 (Day 128, 93.2) and early term (Day 201, 23.3). Neutralizing ab were negative.

As per response to an FDA request for information submitted on 9/2/15, prior to the event of **aseptic meningitis** the patient had diarrhea and intermittent low grade fever and headache for 2-3 weeks. The investigator presumed prolonged viral gastrointestinal infection. He received a 3rd dose of investigational drug in 202 (placebo) and felt well, with persistent mild diarrhea, but then he developed a rash. A friend said he was aggressive and seemed to have mild trouble concentrating. **On physical exam he had a maculopapular rash and a new mild tremor.** MRI showed multiple brain Gd-enhancing lesions that were new or progressing consistent with MS or inflammation. According to the investigator, MRI images were also compatible with **lymphoma**. On hospital admission ((b) (6) weeks into study 202) CSF showed 309 cells/mL (normal up to 5), 3RBC, protein of 1090 mg/L (normal up to 450) and lactate of 3.1 (normal <2.3). Working diagnosis was **meningoencephalitis**. Drug was discontinued. Labs on an unknown date were negative for Borrelia serology, acetylcholinesterase (ACE), beta-glycoprotein, ANA, ENA, C-anti-neutrophil cytoplasmic antibodies, CCP ab, creatinine, globulins, IgG, IgA and IgM. Bone marrow biopsy, CT chest and abdomen, peripheral neurography, ophthalmology, EEG, and Doppler scan were normal. Polymerase chain reaction (PCR) for adenovirus, cytomegalovirus, Epstein Barr virus, John Cunningham virus, BK virus, adeno-associated satellite virus, picornavirus, rubella, and toxoplasma were all also unremarkable. On a follow up report the investigator indicated that human herpes virus and varicella zoster were also unremarkable. His IgE was 1234 U/mL. Total granulocyte count was slightly elevated with 72% neutrophils. The patient was in the hospital (b) (6) The biopsy of the forearm, conducted on (b) (6) showed "irritated subacute eczema." Upon discharge," leukocytes were down from 309 U/ml to 48 U/ml and protein was down from 1195 mg/L to 580 mg/L." The event of aseptic meningoencephalitis considered resolved on May 3, 2011. No steroid treatment was given. No additional information is expected and the case was closed.

Varicella zoster infections (VZV)

203/453-016. Herpes zoster ophthalmicus. Developed blistering rash on face involving first and second branches of the trigeminal nerve on the right, after 43 doses of DAC in study 203. Treated with oral acyclovir without clinical response. She was hospitalized and treated with IV acyclovir for 10 days, with complication of phlebitis at the venous catheter and increased creatinine. She also had edema of the right eyelid and retrobulbar neuritis in the right eye, with evidence of herpes zoster ophthalmicus without injury to the cornea. WBC was 7.5, neutrophils 5.6 and lymphocytes 1.3×10^9 /L. The event resolved and she was discharged home. DAC HYP was interrupted and later resumed.

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203/ 565-003* 15-day IND safety report. 29 M HERPES ZOSTER in the trigeminal area after an unknown number of doses. Treatment started in July 2012. Last dose before the event was April 2015. Lesions were reported as very deep and necrotic with surrounding erythema and edema. Right lower eyelid was swollen but cornea was normal. He was treated with acyclovir and ganciclovir eye ointment. The event resolved with scars by June 2015. At that time he had bilateral eczematous papules and erythematous plaques on both forearms, which was treated with topical treatment. Study drug was not re-started. By August 2015 the lesions had improved but not completely disappeared.

301/741-004 Varicella. 29 F, viral infection, nasopharyngitis, early in the study, two episodes of MS relapse. On Day 225 presented fever, respiratory tract infection and “chicken pox” (Day 355 to 379). She also presented pharyngitis and influenza like illness after the episode of chicken pox diagnosed by dermatologist, treated with acyclovir. Resolved without sequelae. No information on varicella serology before entry. Unclear if this was a new infection or reactivation.

Other viral infections

301/610-003 VIRAL MENINGITIS. 27 male. Day 797 presented mild skin exfoliation followed by macular rash on the body diagnosed as seborrheic dermatitis on Day 814. Viral meningitis was diagnosed on Day 861, and ended on Day 866. No data on evaluation of CSF. Treated with IV fluids and mannitol, no antibiotics or antivirals. Dermatitis lasted until day 1030. Treatment with daclizumab was not discontinued. *In my opinion it is unlikely that a true case of viral meningitis would recover within five days just with IV fluids but unlikely to be DAC related because drug was not stopped (patient received five more doses and completed study).*

- Narratives of non SAE events leading to drug WD in Musculoskeletal system disorders SOC

301/162-002. 39 F ARTHRITIS leading to drug WD on Day 498. This patient had a varied symptoms starting right after the first dose of DAC, with fatigue, headache, 2 episodes of asthma, pneumonia, nephrolithiasis, synovitis, muscle weakness, pain, paresthesia (Day 419-512) and macular rash (Day 480-558) accompanied by arthralgia/arthritis (Day 496-558). She also had oral herpes and hepatic stasis. Last dose of DAC was on Day 475. She was given multiple courses of IV MP throughout the study (from 3 to 7 days, at least at 7 different times). Lab evaluation showed mild increased liver enzymes at baseline; they did not increase during treatment. Patient had multiple symptoms and it is difficult to assess which disease she may have had. There is no information about ANA and RF or calcium measurements. *The relationship to DAC is unclear. How the multiple courses of IV MP for “non-protocol defined” MS relapses impacted this patients’ efficacy assessments is unclear.*

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303/178-005 50 F ARTHRALGIA led to drug WD on Day 69. Patient had hx of urticaria and hypothyroidism. On Day 455 of study 303 had AE of contact dermatitis while on IFN. On Day 69 of DAC she reported polyarthralgia after 3 doses of DAC. DAC was discontinued and patient was treated with diclofenac/paracetamol with resolution of event.

205MS301/543-007 25 M SERONEGATIVE ARTHRITIS led to drug WD. He presented bursal synovitis of the R knee after 25 doses of DAC. He received 3 more doses (last dose on Day 781) but on Day 791 was diagnosed with seronegative arthritis “of joints first and third fingers of right leg” and was treated with diclofenac. It is unclear if this was truly an inflammatory arthritis or not; it appears to have affected knee and toes. This is a young male patient and is unlikely to be a degenerative disease. Drug was discontinued. The event was considered as not resolved.

13.3.12 NEOPLASM DISORDERS, SAE AND DROPOUTS

Table 13.3.12.1.
 Listing of SAE in the Neoplasms SOC on DAC HYP

ID	PT	Age	Sex	Rel day start	Rel day end	Action taken with DAC
Study 201						
306-003	Superficial spreading melanoma stage unspecified	37	F	335	335	NONE
450-005	Cervix carcinoma	41	F	477	596	NONE
458-006	Malignant melanoma	35	F	355	397	NONE
Study 301						
241-001	Uterine leiomyoma	35	F	671	701	WITHDRAW
451-014	Adenoma benign	35	F	662	663	NONE
453-004	Thyroid cancer	49	F	808	811	NONE
492-001	Benign salivary gland neoplasm	39	F	1057	1066	NONE
494-002	Transitional cell carcinoma	53	M	937	952	NONE
537-001	Uterine cancer	49	F	402	NR	WITHDRAW
610-009	Benign neoplasm	42	F	505	553	NONE
610-016	Brain neoplasm malignant	39	F	24	54	WITHDRAW
624-007	Benign ovarian tumor	41	F	457	462	NONE
642-016	Uterine leiomyoma	47	F	100	108	NONE
659-008	Uterine leiomyoma	43	F	607	612	NONE
670-018	Invasive ductal breast carcinoma	45	F	701	NR	WITHDRAWN
678-008	Benign salivary gland neoplasm	19	M	986	989	NONE
706-001	Meningioma	53	F	649	650	NONE
Study 202						
505-010	Breast cancer	45	F	350	NR	NONE
Study 203						
353-001	Intraductal papilloma of breast	36	F	953	968	NONE
453-005	Breast cancer	45	F	1161	NR	WITHDRAWN
454-002	Breast cancer	47	F	1980	NR	WITHDRAWN
508-021	Anal cancer	44	F	869		NONE
751-017	Carcinoid tumor pulmonary	50	M	1072	1131	NONE
909-004	Prolactinoma	24	F	1120	NR	WITHDRAWN
Study 303						
228-002	Abdominal neoplasm	41	F	1119	NR	NONE
451-008	Anorectal HPV infection	27	F	1155	1156	NONE
602-002	Metaplastic breast carcinoma	52	F	1228	1239	WITHDRAW
650-006	Ovarian cancer	52	F	925	NR	WITHDRAWN
657-001	Fibroadenoma of breast	43	F	1354	1367	NONE
670-030	Uterine leiomyoma	26	F	989	1001	NONE

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NR: No end date reported.

Three in the Reproductive neoplasms female malignant HLGT: cervix carcinoma (450-005 in study 201); uterine cancer (537-001 in study 301) and Ovarian cancer in study 303 (650-006). They were 41 to 52 year old females, drug was continued and the event resolved in the case of cervix carcinoma and withdrawn in the case of uterine and ovarian cancer; events are reported as not resolved.

Two endocrine: One thyroid cancer in study 301, (patient 301 453-004, a 49 year old female on Day 808, event reported as resolved) and one pulmonary carcinoid in study 203 (751-017, a 50 year old male on Day 1072 of DAC treatment, event reported as resolved). None of them were thought to be related to treatment and no action was taken with DAC.

One anal carcinoma was reported in the GI malignancy HLGT, an in a 44 year old female, almost 3 years into treatment in study 203. She received DAC 300 in study 201, Placebo/DAC 300 in study 202 and DAC 150 in study 203. No action taken with drug. Event was reported as not resolved. Anal cancer has been associated with HPV infection. There is also a report of a benign anorectal "HPV infection" in this application (451-008 in study 303).

Two cases occurred in the nervous system neoplasms malignant HLGT, both in study 301. One was patient 610-016, a 39 year old female, "malignant tumor of the brain", no pathology provided, reported on Day 24, drug was withdrawn (*unlikely to be related to drug with such a short exposure*); the other was a meningioma (patient 706-001, left cavernous sinus meningioma), in a 53 year old female, on Day 649. Both were on DAC 150. No action was taken with the drug; event was reported as ended on Day 650. *No attribution can be made for a single case.*

One occurred in the renal and urinary tract malignant HLGT: a transitional cell carcinoma in a 53 year old male on Day 937, reported as ended on Day 952 in study 301 (patient 494-002).

Two skin malignancies occurred in this database as of the cut off of the SUR. One was a superficially spread melanoma, in a 37 year old female (306-003) and the other was a malignant melanoma in a 35 year old female (458-006), both in study 201 almost one year into treatment, both on DAC 300 mg. Drug was continued in both cases. *In my opinion, DAC HYP may have played a role, however, apparently drug was continued without recurrence of events.*

Analyses of neoplasms by PT in study 301 are shown below.

Table 13.3.12.2 Patients with neoplasms benign, malignant and unspecified (incl cysts and polyps), study 301

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	DACHYP		IFN	
	n	%	n	%
Any	44	4.8%	34	3.7%
ACROCHORDON	1	0.1%	0	0.0%
ADENOMA BENIGN	1	0.1%	0	0.0%
ANOGENITAL WARTS	2	0.2%	0	0.0%
BASAL CELL CARCINOMA	1	0.1%	0	0.0%
BENIGN BREAST NEOPLASM	1	0.1%	2	0.2%
BENIGN LYMPH NODE NEOPLASM	1	0.1%	0	0.0%
BENIGN NEOPLASM	1	0.1%	0	0.0%
BENIGN NEOPLASM OF THYROID GLAND	1	0.1%	0	0.0%
BENIGN OVARIAN TUMOUR	1	0.1%	0	0.0%
BENIGN SALIVARY GLAND NEOPLASM	2	0.2%	0	0.0%
BRAIN NEOPLASM MALIGNANT	1	0.1%	0	0.0%
BREAST FIBROMA	0	0.0%	1	0.1%
DYSPLASTIC NAEVUS	1	0.1%	1	0.1%
ENDOMETRIAL CANCER	0	0.0%	1	0.1%
FIBROADENOMA OF BREAST	1	0.1%	4	0.4%
FIBROMA	1	0.1%	1	0.1%
FIBROUS HISTIOCYTOMA	0	0.0%	1	0.1%
HAEMANGIOMA OF LIVER	3	0.3%	1	0.1%
INVASIVE DUCTAL BREAST CARCINOMA	1	0.1%	0	0.0%
LIP SQUAMOUS CELL CARCINOMA	1	0.1%	0	0.0%
LIPOMA	3	0.3%	0	0.0%
MALIGNANT MELANOMA	0	0.0%	1	0.1%
MELANOCYTIC NAEVUS	2	0.2%	3	0.3%
MENINGIOMA	2	0.2%	0	0.0%
NEUROFIBROMA	0	0.0%	1	0.1%
NEUROMA	0	0.0%	1	0.1%
OVARIAN GERM CELL TERATOMA BENIGN	0	0.0%	1	0.1%
PANCREATIC CARCINOMA METASTATIC	0	0.0%	1	0.1%
PITUITARY TUMOUR BENIGN	0	0.0%	1	0.1%
SEBORRHOEIC KERATOSIS	2	0.2%	2	0.2%
SKIN PAPILLOMA	4	0.4%	2	0.2%
SQUAMOUS CELL CARCINOMA	0	0.0%	1	0.1%
SQUAMOUS CELL CARCINOMA OF THE CERVIX	0	0.0%	1	0.1%
SQUAMOUS CELL CARCINOMA OF THE ORAL CAVITY	0	0.0%	1	0.1%
TESTICULAR SEMINOMA (PURE)	0	0.0%	1	0.1%
THYROID CANCER	1	0.1%	0	0.0%
THYROID NEOPLASM	1	0.1%	0	0.0%

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TONGUE NEOPLASM MALIGNANT STAGE UNSPECIFIED	0	0.0%	1	0.1%
TRANSITIONAL CELL CARCINOMA	1	0.1%	0	0.0%
UTERINE CANCER	1	0.1%	0	0.0%
UTERINE LEIOMYOMA	12	1.3%	8	0.9%

Source: Empirica Study.

Table 13.3.12.3 Patients with malignant neoplasms in study 301

	DAC150 N=919		IFNβ1a N=922	
	n	%	n	%
ANY patient with any Malignant neoplasm	10	1.1%	8	0.9%
BREAST NEOPLASMS MALIGNANT AND UNSPECIFIED (INCL NIPPLE)	1	0.1%	0	
invasive ductal breast carcinoma	1		0	
ENDOCRINE NEOPLASMS MALIGNANT AND UNSPECIFIED	2	0.2%	0	
thyroid cancer/thyroid neoplasm	2		0	
GASTROINTESTINAL NEOPLASMS MALIGNANT AND UNSPECIFIED	1	0.1%	3	0.3%
squamous cell ca or oral cavity	0		1	
pancreatic carcinoma metastatic	0		1	
tongue neoplasm malignant	0		1	
lip squamous cell carcinoma	1		0	
MISCELLANEOUS AND SITE UNSPECIFIED NEOPLAS MALIGNANT AND Uns	0	0.0%	1	0.1%
squamous cell carcinoma	0		1	
NERVOUS SYSTEM NEOPLASMS MALIGNANT AND UNSPECIFIED NEC	3	0.3%	0	0.0%
brain neoplasm malignant	1		0	
meningioma	2		0	
RENAL AND URINARY TRACT NEOPLASMS MALIGNANT AND UNSPECIFIED	1	0.1%	0	0.0%
transitional cell carcinoma	1		0	
REPRODUCTIVE NEOPLASMS FEMALE MALIGNANT AND UNSPECIFIED	1	0.1%	1	0.1%
endometrial cancer	0		1	
REPRODUCTIVE NEOPLASMS MALE MALIGNANT AND UNSPECIFIED	0		1	0.1%
testicular seminoma	0		1	
SKIN NEOPLASMS MALIGNANT AND UNSPECIFIED	1	0.1%	1	0.1%
basal cell ca	1		0	
malignant melanoma	0		1	

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Source: MO analysis using JMP, Study 301 AE datasets.

Neoplasms in the Total DAC HYP database are summarized below, by HLGT.

Table 13.3.12.4 Neoplasms in Total DAC HYP by HLGT

Patients with any event in SOC	104
CUTANEOUS NEOPLASMS BENIGN	30
REPRODUCTIVE NEOPLASMS FEMALE BENIGN	25
BREAST NEOPLASMS BENIGN (INCL NIPPLE)	6
BREAST NEOPLASMS MALIGNANT AND UNSPECIFIED (INCL NIPPLE)	6
SOFT TISSUE NEOPLASMS BENIGN	6
ENDOCRINE NEOPLASMS BENIGN	5
ENDOCRINE NEOPLASMS MALIGNANT AND UNSPECIFIED	5
HEPATIC AND BILIARY NEOPLASMS BENIGN	4
MISCELLANEOUS AND SITE UNSPECIFIED NEOPLASMS BENIGN	4
SKIN NEOPLASMS MALIGNANT AND UNSPECIFIED	4
GASTROINTESTINAL NEOPLASMS BENIGN	3
NERVOUS SYSTEM NEOPLASMS BENIGN	3
NERVOUS SYSTEM NEOPLASMS MALIGNANT AND UNSPECIFIED NEC	3
REPRODUCTIVE NEOPLASMS FEMALE MALIGNANT AND UNSPECIFIED	3
GASTROINTESTINAL NEOPLASMS MALIGNANT AND UNSPECIFIED	2
HAEMATOPOIETIC NEOPLASMS (EXCL LEUKAEMIAS AND LYMPHOMAS)	2
MISCELLANEOUS AND SITE UNSPECIFIED NEOPLASMS MALIGNANT AND UNSPECIFIED	1
RENAL AND URINARY TRACT NEOPLASMS MALIGNANT AND UNSPECIFIED	1
REPRODUCTIVE NEOPLASMS MALE BENIGN	1
RESPIRATORY AND MEDIASTINAL NEOPLASMS BENIGN (EXCL MESOTHELIOMAS)	1
RESPIRATORY AND MEDIASTINAL NEOPLASMS MALIGNANT AND UNSPECIFIED	1

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13.3.13 NERVOUS SYSTEM DISORDERS SOC, SAE AND DROPOUTS

Listing of patients with SAE in the neuro SOC other than MS/MS relapse, DAC controlled studies

ID	Treatment	PT	Age	Sex	Intensity	Action taken	Onset day	End day
Study 201								
363-004	DAC 300	Intracranial aneurysm	41	F	SEVERE	NONE	260	303
509-017	DAC 150	Cerebrovascular insufficiency	39	M	MILD	NONE	114	115
559-008	DAC 300	Migraine	32	M	MILD	NONE	322	330
752-010	DAC 300	Syncope	36	M	MOD	WITHDRAWN	1	1
Study 301								
116-001	DAC 150	Migraine	50	F	SEVERE	NONE	633	634
123-009	DAC 150	Complex partial seizures	54	M	MOD	NONE	503	503
125-005	DAC 150	Convulsion	52	M	MOD	INTERRUPTED	694	697
133-004	DAC 150	Headache (<i>see narrative below</i>)	51	F	SEVERE	NONE	123	126
141-009	DAC 150	Uhthoff's phenomenon	36	F	MOD	NONE	318	341
161-004	DAC 150	Toxic encephalopathy	53	F	MOD	NONE	512	514
407-001	DAC 150	Dizziness	26	M	MOD	NONE	111	141
544-013	DAC 150	Convulsion	35	M	SEVERE	NONE	823	828
600-017	DAC 150	Status epilepticus	47	F	SEVERE	WITHDRAWN	429	450
608-007	DAC 150	Convulsion	21	F	MILD	NONE	249	254
612-010	DAC 150	Sciatica	52	F	MOD	NONE	672	675
617-004	DAC 150	Convulsion	20	M	MILD	NONE	580	583
629-008	DAC 150	Transient ischemic attack	51	M	MOD	NONE	652	673

Study 202								
509-014	Placebo/ DAC 300	Demyelination	40	F	MOD	NONE	347	361
758-023	Placebo/ DAC 300	Ischemic neuropathy	39	F	MOD	NONE	353	368
761-003	Placebo/ DAC 300	Hemorrhagic stroke	38	M	SEVERE	DOSE INTERRUPT	505	534
Study 203								
303-006	Placebo/	Headache	42	F	MOD	NONE	828	

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	DAC150							
353-001	DAC300/ Pbo-AC300/DAC150	Grand mal convulsion	36	F	SEVERE	NONE	1749	1749
505-026	DAC 150/Pbo-DAC150/DAC 150	Neurological decompensation	53	F	MOD	NONE (<i>had already WD</i>)	1595	1603
Study 303								
159-004	IFNβ1a/DAC150	Convulsion	45	F	SEVERE	NONE	269	269
455-007	DAC150/DAC150	Syncope	25	M	SEVERE	NONE	1024	1026
537-012		Brain compression			SEVERE	NONE	1058	1060
		Brain edema				WITHDRAWN (fatal)		
544-013		Epilepsy			MODERATE	NONE	936	941
600-010	DAC 150/DAC 150	Myasthenia gravis	51	M	MODERATE	WITHDRAWN	997	1214
611-015	DAC150	Epilepsy			MODERATE	NONE	1193	-
657-016	IFNβ1a/DAC 150	Epilepsy	24	M	MODERATE	NONE NONE	112 260	113 260
659-001	DAC 150/DAC 150	CEREBRAL VENOUS THROMBOSIS and Epileptic seizure	29	F	SEVERE	NONE (<i>already WD for sarcoid</i>)	1115	1135
731-001	DAC150	Neurological symptom			MODERATE	NONE	1462	1463

Source: ADAE3 dataset, SUR.

301/133-004. 51 F. Prior history in this patient included asthma, hypothyroidism and hypertension. On day 119 she started to have bilateral temporal headaches. SAE of bitemporal headache on Day 123 to 126. On Day 260 presented maculopapular rash on face and chest, that eventually led to drug withdrawal and resolved on Day 439. Last day on drug: Day 338. *I am including the narrative because when reviewing the patient profile I found that this patient underwent a temporal artery biopsy on study Day 124. She was treated with high dose prednisone 60 mg/day, with tapering down to 10 mg/day on Day 145. Apparently prednisone was stopped without tapering without recurrence of symptoms. The patient continued in the study and received IFNβ as alternative MS therapy. She also received several courses of methylprednisolone for non protocol defined MS relapse, bronchitis and shingles. As per follow up information submitted 3/3/16, the biopsies did not reveal “active temporal arteritis”, but the patient was treated with corticosteroids on the recommendation of the treating ophthalmologist who suspected temporal arteritis clinically.*

Cases of SAE of seizures on DAC HYP 150 in study 301 are summarized below.

301/123-009. 54 M, complex partial seizure of moderate intensity on Day 503. Recovered the same day. He was started on lamotrigine. He had no history of seizures. Prior MS meds included betaseron, glatiramer, mitoxantrone and natalizumab. Concomitant meds at the time of the seizure included modafinil, escitalopram and gabapentin (for peripheral neuropathy) which were taken prior to entering the study. Baseline EDSS was 4.0. He had one MS relapse on day 176 and no further MS relapses. No action taken with drug. He completed the study. EDSS at end of study was 3.5. Patient entered study 303 and received 7 doses of DAC before stopping. Seizure does not appear related to worsening MS.

301/125-005. 52 M. Convulsion of moderate intensity on Day 694, resolved on Day 697. He had a history of coronary artery disease, restless leg syndrome, insomnia and depression. No history of seizures. Baseline EDSS score was 3.5. No MS relapses during study. He had taken various medications to treat the above mentioned conditions. He was treated with baclofen for pain and spasms from Day 673 to 694. Baclofen was discontinued. Seizures were treated with levetiracetam. DAC 150 is listed as interrupted but he did not receive any dose after the seizure. He did not complete treatment. Last dose was on Day 673. Reason for withdrawal was Investigator's decision for medical reasons and non-compliance. By Day 733 at the Early termination visit the EDSS score was 4. *Baclofen appears to be a possible confounding factor.*

301/544-013. 35 M. Convulsion of severe intensity on Day 823, resolved day 828. No action taken with DAC. He had no significant medical history including not history of seizures. EDSS at baseline was 2.0. He did not have any relapse during the study. No treatment was given for seizure. He received one additional dose of DAC on Day 842. He completed the study (EDSS score was unchanged) and entered the extension study. One SAE of convulsion was reported in study 303. *Seizure does not appear to be related to worsening MS.*

301/600-017. 47 F, severe status epilepticus on Day 429, resolved on Day 450. DAC withdrawn. Last dose was on Day 421. No significant medical history. Previously treated with fumaric acid. Baseline EDSS was 4.5. She had a non-protocol defined MS relapse Days 223 to 230), a MS relapse on Day 230-236 (treated with IV MP) and another non-protocol defined MS relapse on Day 429 along with "epilepsy secondary generalized" and status epilepticus. Epilepsy was treated with levetiracetam and valproic acid, starting sometime in 2012, it is unclear for how long (no date stated; the first dose of DAC had been 9/29/11). Episode on Day 429 was treated with diazepam, IV MP, levetiracetam, valproate, baclofen (429-450). At early termination on Day 484, EDSS was unchanged from baseline. *It is unclear if the first "non-protocol defined MS relapse" was a seizure and what symptoms she had as part of the protocol defined relapse. Perhaps related to worsening MS.*

301/608-007. 21 F. mild convulsion on Day 249, resolved Day 254. No action taken with DAC.

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No significant medical history. No history of seizures. Prior treatment with interferon beta 1b. Baseline EDSS was 3.0. She was hospitalized due to seizure on Day 249 to Day 254. Epilepsy was diagnosed on Day 252 and not resolved. She had one episode of MS relapse on Day 282 to 288. She was treated with carbamazepine Days 252-284, and IV PM Days 284-288. She did have an adverse event of LFT elevation on Day 337 with ALT & AST 4xULN, normal BR (day of last dose of DAC). She withdrew consent to participate in the study. At early termination (Day 420) EDSS was 4. Liver enzymes had resolved. *This case may be related to worsening MS.*

301/617-004. 20 M. moderate non-serious convulsion on Day 570 and mild, serious convulsion on Day 580, resolved Day 583. The event occurred after 25 doses of DAC HYP 150. “No action taken with DAC”. No significant medical history, no history of seizures. EDSS at baseline 1.5. Had transient mild elevated transaminases Day 393-400 (DAC interrupted x 1 dose). BP at baseline was 127/88. SBP increased over time, around 140/90 by week 12 (Day 83). Hypertension diagnosed Day 580, treated with Ramipril. Completed the study. EDSS at the end was unchanged from baseline. ECG normal. No drug listed for treatment of serious “convulsion”. *Unclear if the first was a convulsion but there was a second one. It does not seem to be related to worsening MS. As per the disposition dataset for study 303 the patient entered 303 but dropped out after one dose.*

Narratives of patients with seizure events on IFNβ1a in 301 suggest that they were related to worsening MS. One occurred after documented worsening EDSS (301/514-005); the other (301/604-037) occurred as part of an event of MS relapse/worsening MS.

Additional SAE of seizure occurred in extension studies, as follows.

202/353-001. 36 F, who had received DAC HYP 300 in study 201, and placebo followed by DAC HYP 300 in study 202. She presented severe AE of grand mal convulsion on Day 1749. No action taken with drug.

303/159-004. 45 F hx of fatigue, spasticity, allergy to Augmentin, received IFNβ1a in 301 and DAC HYP 150 in 303. During 301 she presented urticaria described as pruritic and burning. She entered study 303 and presented severe convulsion on Day 269 after 10 doses of DAC HYP. She was sitting drying her hair, fell and hit her head. The convulsion lasted 1 minute and resolved on the same day. “No action was taken with drug.” CT no acute bleeding. Patient had some initial postictal confusion but was alert at the time of the re-evaluation. The examination did not reveal any focal neurologic abnormalities, and the subject did not appear to have an underlying cause for the seizure. She started treatment with levetiracetam for seizure prophylaxis. However, on Day 281 the treating and no-study neurologists recommended to stop drug. A brain MRI showed chronic demyelinating process, a **new large lesion** involving the subcortical left frontal lobe and a large active plaque. Additional treatment included temazepam, Vitamin D, and methylprednisolone. The investigator reported that the cause of the seizure was not known but was possible related to active MS. *Again one case in which the*

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dataset says “no action taken” but the drug was in fact stopped because of the event. In this case seizure seems to be caused by a new MS plaque.

303/657-016, 24 M, who received IFNβ1a in 301 and DAC 150 in 303, with a history of asthma developed **epilepsy**, considered to be moderate, with one episode of seizure on Day 112 to 113 (after 4 doses of DAC HYP) and another one on Day 260 (after 9 doses of DAC HYP). No history of personal or family history of seizures, denied use of illicit drugs or alcohol or recent head injury. Concom medications at the time of the seizure was fenoterol. Patient woke up with a seizure, with disorientation and incontinence. At the hospital labs were within normal except for mild leukocytosis. CT scan and ECG were normal. No action taken with drug. Cause of the event was considered to be MS. Subsequently, on Day 224 of study 303 the patient presented dermatitis allergic that was classified as non-serious but led to study withdrawal after 9 doses of DAC HYP (last dose was given on Day 222). She was treated with diazepam, ergenyl, methylprednisolone and omeprazole. The event of dermatitis resolved on Day 317. A second epileptic seizure was reported on Day 260, approx. 40 days after the last dose of DAC HYP.

303/657-016 24 M, new onset seizure. He received 3 years of IFNβ1a in 301 and 9 doses of DAC 150 in 303. He did have flu-like symptoms, upper respiratory infections, and moderate rash leading to drug interruption in study 301. His EDSS went from 1.5 at entry to 0 on week 144 (day 1010). He had one episode of MS relapse at the end of 301, on Day 1018 (not resolved). He was treated with IV MP for 4 days starting on Day 1 of study 303. The subject had received 4 doses of DAC HYP in Study 205MS303 before onset of the event, with his most recent dose given on (b) (6) (Day 85). Episode of epileptic seizure was reported on Day 112 to 113 of study 303, along with disorientation and incontinence. The subject was subsequently hospitalized treated with diazepam. Labs were within normal. DAC antibody negative. A CT of the head was normal. MRI was not done. The etiology of the subject's seizures was reported as multiple sclerosis. An update received after the interim database lock indicated that the subject experienced another epileptic seizure and was hospitalized (b) (6). The Investigator considered the event (epilepsy) to be unrelated to study treatment. It is unknown if the patient continued in the study or was withdrawn.

The following case of ischemic neuropathy was treated with neostigmine for unclear reasons.

202/758-023 40 F developed ischemic neuropathy on Day 353, after placebo in 201 and 13 doses of DAC 300 in 203. She had a “compressive ischemic neuropathy of right tibial nerve.” subsequent to a fall and traumatic injury. Treatment was withdrawn. Last dose was on Day 339 (14 days prior to onset of the event). Treatment included neostigmine among other drugs from Days 365-368. Ischemic neuropathy was considered resolved and patient was discharged from the hospital. DAC abs was negative on Day 0 and 85, and positive on Days 141, 226, and 367 (with titers of 18.6, 46.6 and 92.2 respectively) and Day 283 (no quantification).

Neostigmine is a parasympathomimetic that acts as a reversible acetylcholinesterase inhibitor. The typical indication for neostigmine is Myasthenia Gravis and colonic ileus, none of which

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were apparently reported in this patient. As per response to a request for clarification, the applicant does not know why the patient received neostigmine.

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13.3.14 PREGNANCY, PSYQUIATRIC and RENAL DISORDERS, SAE AND DROPOUTS IN

13.3.14.1 Pregnancy related SAE

301/435-004	29F, after 22 doses; abortion spontaneous/ectopic pregnancy. Patient had a hx of one miscarriage and two live births. She had one episode of MS relapse treated with IV MP on Day 19. Also received paracetamol. Approx. 1 month after stopping oral contraceptive she had positive plasma hCG level indicating pregnancy. US showed a normal fetus. One month later she had a spontaneous abortion (Day 656, estimated gestational age 8 weeks) treated with curettage.
301/472-003	33F, after 8 doses of DAC; abortion spontaneous. Hx of prior miscarriage. Patient was taking an oral contraceptive but plasma hCG was positive. Drug was WD because of pregnancy. 8 weeks after her last menstrual period patient had vaginal bleeding; US confirmed no fetal heartbeat. Curettage was performed.
301/604-064	32F, after 25 doses; ectopic pregnancy diagnosed at gestational age of 10 weeks upon failed contraception. She had two children and no prior abortion. Patient underwent elective termination and continued receiving DAC HYP.
202/110-006	24F, after 20 doses of DAC 150. Abortion spontaneous, drug withdrawn. Hx of hypothyroidism on levothyroxine. Pregnancy attributed to failed male (condom) contraception was detected at 6 weeks of gestational age. On a regular prenatal checkup, US showed missed abortion of approx. 9 weeks gestational age. Last dose of DAC had been 2 months prior.

SUMMARY OF PREGNANCIES (NOT ADVERSE EVENTS).

<i>ID</i>	<i>Comment/outcome</i>
301/557-001	25 F, hx of left sided anexitis. She received 24 doses of DAC HYP. She had 1 living child and no abortions. Contraceptive was condoms and spermicide. Last menstrual period (LMP) was in December 2013. On (b) (6), urine hCG was positive; ultrasound confirmed pregnancy. Drug was discontinued. Last dose was Jan 14, 2014. Estimated delivery date 2as September 2014. PATIENT WAS LOST TO FOLLOW UP.
301/572-001	38 F. She received 22 doses of DAC HYP. Last dose was Jan 31, 2014. She had one live child. Contraceptive history was use of condoms. LMP was Feb 20, 2014. She received 2 doses of DAC. On (b) (6) an ultrasound confirmed her pregnancy. Drug was discontinued. She gave birth to a live infant at 40 weeks gestation without complications or defects.
301/611-022	25 F. Concom meds: desogestrel. She received 35 doses of DAC HYP. His of 1 child and no abortions. LMP was March 6, 2014. On (b) (6) an US

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	confirmed pregnancy. She started treatment with folic acid and progesterone. She gave birth to a live infant at 40 weeks gestation without complications or defects. Apparently “no action was taken with study drug,” and she completed the study, but the final assessment was May 17, 2014. Therefore, in fact, drug was not continued.
301/618-005	24 F. Meds included tizanidine and oxybutynin. She received 27 doses of DAC. No pregnancy history. LMP was Nov 28, 2013. On (b) (6) urine hCG was positive. Prior to this date she had received 1 dose of AC (Dec 9, 2013). Drug was discontinued. US confirmed pregnancy and she started treatment with folic acid. She gave birth to a live infant at 37 weeks of gestation via C section without reported complications, defects or infections.
203/564-002	31 F. She received 32 doses of DAC HYP. Last dose was Nov 11, 2014. Hx of prior pregnancies not reported. LMP was December 17, 2014. On Jan 17, 2015 serum hCG test was positive. Contraceptive method no reported. ACTION TAKEN WITH TREATMENT AND OUTCOME OF PREGNANCY is UNKNOWN.
203/501-004	Received 43 doses of DAC. She had two living children and no prior abortions. Contraception was spermicide cream. Diagnosis was made by positive hCG test. Gestational age at time of diagnosis was 4 weeks. Drug was withdrawn. Baby was born without complication; no major congenital malformations.
303/412-017	36 F. She received 4 doses of DAC. No prior births or terminations. Used condoms and spermicide as contraception. Last menstrual period June 5 2014. Last dose was June 12, 2014. hCG was positive on July 10, 2014. Gestational age 5 weeks. Drug discontinued. OUTCOME FOR PATIENT AND BABY NOT AVAILABLE.
303/441/-019	26 F. She received 11 doses of DAC. No history of prior pregnancies. Last dose November 214, 2014. Contraceptive implant. Last menstrual period Nov 17, 2014. hCG pregnancy test positive on December 24, 2014 (Gestational age 5 weeks). Subject underwent elective termination at 9 weeks. Status of patient not available.
303-453-016	36 F. History of goiter taking multiple medications (venlafaxine, levothyroxine, alprazolam, oral contraceptive [drospirenone with ethynylestradiol]). She had one living child. LMP was Nov 25, 2013. She received two doses of DAC (Nov 28 and December 30, 2013). hCG pregnancy test was positive on Jan 3, 2014. (Gestational age 5 weeks). She gave birth to twins via elective cesarean section at 32 weeks. The subject and children were reported in good health.

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13.3.14.2 Selected Psychiatric SAE

01/ 302-007	SUICIDAL IDEATION	47F after, SAE after 14 doses of DAC HYP 150. Prior hx of depression. Event reported Day 360 to 364 of study 301. Led to drug WD.
302/ 162-106	SUICIDE ATTEMPT	46F, SAE on Day 267 after 25 doses of DAC HYP 150. No action taken with drug. As per datasets, event lasted 44 days. This patient had depression and was taking fluoxetine prior to entering the study
303/ 609-029	SUICIDE ATTEMPT	40F, SAE after 36 doses of DAC HYP 150 in study 303. Hospitalized Day 826 to 828. No action taken with drug.
301/ 128-003	DEPRESSION SUICIDAL	40 F, SAE after 15 doses of DAC HYP 150. Verbatim was “suicidal attempt due to severe depression.” She had severe MS and a prior history of depression. Medications at the time of the event included alprazolam, metoprolol, venlafaxine and quetiapine. The event of “depression suicidal” was reported on Day 404 along with “hypotension due to beta-blocker overdose”. She was treated in the ICU for multi-drug overdose with insulin, glucose and dopamine. Event resolved on Day 420. No action was taken with DAC.
203/ 453-010	DEPRESSION (suicidal attempt not captured in dataset)	38 F, after 67 doses of DAC HYP 150. Hx of alcohol abuse. As per the datasets, this patient had SAE of depression leading to drug interruption. However, as per the narrative she had suicide attempt with alcohol and benzodiazepines and started valproate. 1 ½ month later she had drug induced hepatitis that led to drug withdrawal. <i>Case discussed under Hepatobiliary SAE.</i>

13.3.14.3 Selected SAE in Renal Disorders SOC – cases of lithiasis

201/ 559-004	35 F. Nephrolithiasis (bilateral renal lithiasis mild severity) after 69 doses of DAC HYP 300 Days 253-258. Dose interrupted.
301/ 130-002	53 M. Nephrolithiasis (worsening of previous condition) after 53 doses of DAC HYP 150. Day 65 to 121 (duration almost 2 months). It was considered severe but no action was taken with drug.
301/	39 F. Nephrolithiasis (kidney stones) after 18 doses of DAC HYP 150. Day 283-289. Moderate. No action taken. Other AEs

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162-002	during study: fatigue, urinary tract infection, bilateral leg edema, lobar pneumonia, asthma, mild synovitis of hands and feet, paresthesia, macular rash, arthralgia, arthritis. Many of these AE reported as not resolved. Arthritis led to drug withdrawal, treated with oral prednisone. Also had several episodes of MS relapse, treated with IV MP.
301/604-059	30 M. Nephrolithiasis (left side) after 34 doses of DAC HYP 150. Day 200 to 262 (almost 2- month duration). Prior Hx of nephrolithiasis and lithotomy. Dose interrupted. Pt underwent lithotripsy.
301/604-030	21 F. Renal colic after 33 doses of DAC 150, severe, Day 283-285, no action taken with drug
303/658-006	41 M. renal colic, after 44 doses of DAC 150, two separate episodes, each lasted 4 and 7 days, respectively. No action taken with drug.
303/457-004	47 F. Calculus ureteric after 7 doses of DAC HYP 150 (patient had IFNβ1a in 301). Moderate, Day 449 to 455. No action taken with drug.

13.3.15 RESPIRATORY DISORDERS SOC, SAE and DROPOUTS IN

ID	PT	Age/sex/action taken with drug/ Comment
Study 301		
105-006	PULMONARY EMBOLISM	49 F. Patient had a fall on Day 658 after 24 doses of DAC and had tibial and fibular fracture, requiring surgery. She received one more dose on Day 679. She was taking calcium and warfarin sodium. On Day 702 she had pleuritic chest pain and was diagnosed with bilateral PE. Event resolved on day 872. Duration 171 days. Dose interrupted bur she continued treatment and completed the study.
162-002	ASTHMA	Day 524-527 In patient with lobar pneumonia. <i>See narrative under Infections SOC</i>
239-001	PULMONARY EMBOLISM	21 F, hx of dysmenorrhea, depression, asthma, hypoglycemia. At the time of the event she was on an oral contraceptive. On Day 63 presented pleuritic chest pain diagnosed as PE (CT angiography), treated with enoxaparin and warfarin. Event resolved on Day 109. Duration 47 days. DRUG WITHDRAWN because of administrative reasons.
457-001	INTERSTITIAL LUNG DISEASE	37 F. Hx of allergic rhinitis and smoking. Prior treatment included IFN beta 1a and natalizumab. She developed interstitial pneumonia that responded to antibiotics and was improving at the time of last follow up, when she withdrew consent to continue in the study.

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	<i>(interstitial pneumonia)</i>	In May 2013 she reported cough, which worsened. On (b) (6) (Day 721) she saw a pneumologist. Spirometry showed mixed ventilator failure with subclinical obstruction responding to bronchodilators. She was diagnosed with interstitial pneumonia after 25 doses of DAC. Treated with betamethasone, clarithromycin, deflazacort and moxifloxacin. A CT scan did not show interstitial abnormalities or lymphadenopathy. Spirometry repeated on (b) (6) showed that subclinical obstruction was still present after a month of acute lower respiratory infection and mild emphysema. Beclometasone and femoterol were added. In August 2013 the subject withdrew consent and discontinued from the study. The event was considered resolved with sequela of slight exertional dyspnea. Duration 69 days. <i>It is difficult to decide how to best code this event. It appears that the CT scan did not show interstitial changes. This could have been atypical pneumonia. The case is confounded by a history of smoking. As per AE dataset drug was interrupted in May 2013, but in fact drug discontinued as no further doses were given after the event. As per additional information submitted 10/15/15 she had no mediastinal lymphadenopathy; ESR, CBC and CReactive protein were within normal. Treated with Betamethasone Day 721-726 and Deflazacort 15 mg on Day 731 (unclear for how long)</i>
744-007	PNEUMONIA ASPIRATION	Day 95 to 202. Duration 108 days. Patient developed sepsis and died. <i>See narrative under Infections SOC.</i>
Study 202		
450-003	PULMONARY EMBOLISM	36 F. Received 13 doses of DAC 300 mg in 201 and 6 in 202. On Day 159 of 202 presented DVT of left ileo femoral vein, along with pulmonary embolism, confirmed by CT scan, treated with thrombolytic therapy, enoxaparin and warfarin. Duration 20 days. She had a prior hx of DVT and factor V Leiden mutation. Patient continued DAC treatment.
554-001	PULMONARY GRANULOMA	24 F. Event onset: Day 38 to 525. Received 13 doses of placebo in 201, and 2 doses of DAC 150 in study 202 before hospitalization with fever, cough and suspected viral pneumonia on (b) (6) Chest X-ray showed no clear infiltrates but cloudiness in the upper third of the R lung. CRP was 99 mg/L (normal up to 7.5). ALT was 3xULN and AST 2xULN. She improved after treatment with roxithromycin and levofloxacin but had persistent cough. CT of Chest 3 weeks after initial presentation showed miliary lung pattern in the R lung with mediastinal lymph nodes along the aortic arch and esophagus. No hilar adenopathy.

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		<p>Multifocal miliary shades suggested TB. A bronchoscopy showed chronic bronchitis. DAC HYP was discontinued. She was hospitalized again (b) (6) for video assisted thoracic surgery with lung biopsy that showed “inflammatory granulocytosis pulmonis” coded as “Pulmonary granuloma”. On April 2011 the event was considered resolved. A CT of the chest (b) (6) showed residual shadow in her right lung. Total duration: 215 days.</p> <p><i>It is unclear to me if the coding is appropriate. She had miliary granulomas, not a single granuloma. In response to a request for clarification the applicant confirmed that the diagnosis was “inflammatory granulocytosis”. Lab evaluation showed CRP of 99.4 (very high). There is no information about other lab evaluations such as CBC and differential. Complement and autoantibodies were not obtained. BAL and LN bx were not done. Symptoms and radiological findings showed full regression. It is unclear if the patient received steroids or not. The original safety report states that she did; on a safety FU the investigator said she did not receive steroids. The investigator thought that the event was related to DAC.</i></p>
Study 203		
563-001	IDIOPATHIC PULMONARY FIBROSIS	<i>See narrative after table.</i>

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751-015	INTERSTITIAL LUNG DISEASE	<p>42 M. Had pneumonia on Day 1052 of study 203. He received 13 doses of DAC 300 in study 201, 5 of placebo and 8 of DAC 300 in 202; then 37 doses of DAC 150 in study 203. Concomitant conditions included chronic gastritis and neurocirculatory dystonia. Conc. meds included hydroxyzine, pyridostigmine. The last dose of DAC in study 203 was received on (b) (6). On day 1052 (b) (6) he was hospitalized with left side pneumonia. Chest X-ray showed multiple infiltrative shadows in lungs and hyperplasia of mediastinal lymph nodes. Bronchoscopy showed bilateral diffuse bronchitis. The physician thought it could be sarcoidosis. On (b) (6) he was diagnosed with bilateral interstitial lower lobe pneumonia with pleural effusion. Treatment included metronidazole, ceftriaxone, ciprofloxacin, sulfadimidine, linezolid, aminophylline and ambroxol. He was discharged on (b) (6) (3 months after last dose of DAC). Pneumonia resolved with sequelae. <i>Unclear if this was an infection or immune mediated lung disease.</i></p>
Study 303		
611-015	RESPIRATORY FAILURE	<p><i>In patient with aspiration pneumonia and septic shock. See narrative under Infections (sepsis).</i></p>
611-029	PULMONARY SARCOIDOSIS	<p>22 male. Had intermittent low grade fever, lymphadenopathy, arthralgias and mild AST elevation, lymphopenia and submandibular and cervical lymphadenopathy between Days Day 600 and 994 in study 301. Also had. Last dose in 301 was on Day 980. He had eosinophilia on Day 1 of study 303 (b) (6) elevated LDH, lymphadenopathy and arthropathy. He was diagnosed with pulmonary sarcoidosis on Day 16 of study 303 ((b) (6), Day 1023 of DAC). DRUG WITHDRAWN. Treated with methyl prednisolone 40 mg/day for 2 weeks in May-June 2014, followed by oral prednisone. Received prednisone 20 mg/ day since June 2014, for unclear duration.</p>
658-006	DYSPHONIA	<p>Onset on Day 632. No end date. In patient who had hypersensitivity reactions. <i>See narrative under Immune system disorders.</i></p>
670-021	COPD	<p>CHRONIC OBSTRUCTIVE PULMONARY DISEASE Day 50 to 57. No action taken with drug.</p>
Study 302		

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622-502 *	INTERSTITIAL LUNG DISEASE SARCOIDOSIS	54 F. Submitted as 15-day report in July 2015. Past Hx of one episode of bilateral pneumonia and tinea versicolor. Concomitant conditions: Grave's disease, headache, herpes, urinary infections. Concom med: levothyroxine, furosemide, escitalopram. Started DAC HYP in (b) (6). Event was on (b) (6) 18 months into treatment (number of doses is unknown). She presented nodules in both arms. Histopathology results showed non caseating granuloma of the dermis and subcutaneous tissue consistent with sarcoidosis. HRCT in (b) (6) showed interstitial lung disease and hilar lymphadenopathy. Spirometry showed decreased FEV1 and BAL showed eosinophils and lymphocytes interpreted as "consistent with mild asthma or eosinophilic pneumonia." There was no peripheral eosinophilia. Drug was discontinued in (b) (6). <i>NEEDS FOLLOW UP of treatment and outcome.</i>
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203/563-001 50 F. She received DAC HYP 150 in 201 and 202 (total of 24 doses) and 5 more doses in study 203 before the event of "alveolitis". She presented bronchopneumonia on Day 406 of study 202. Treatment included levofloxacin, theophylline, methylprednisolone (IV followed by oral) and moxifloxacin. The event was considered resolved a month later. On Day 100 of study 203 she had another event of bronchopneumonia. Treatment included levofloxacin and oral MP. Event resolved a month later. On Day 131 of study 203 she was diagnosed with **alveolitis and mediastinal lymphadenopathy** as per CT scan of chest (report not provided). Test for TB was negative. She was diagnosed with inflammatory process in the lungs and mediastinum. Treated with levofloxacin (August 14 to December 2, 2012) without response. Pulmonary inflammation increased in size on X-ray, therefore drug was discontinued. The last dose was administered (b) (6). A CT showed "Unchanged lymph nodes" and "progression in the lungs". In (b) (6) she underwent thyroidectomy for goiter. On (b) (6) she underwent **thoracoscopy and lung biopsy** with diagnosis of **idiopathic pulmonary fibrosis**. Treatment included oxybutynin, nadroparin, aminophylline, amoxicillin and theophylline. The event was considered resolved on (b) (6) (Day 460) and the patient was discharged home. The narrative notes that goiter was diagnosed as an incidental finding during one of the episodes of bronchopneumonia in October 2011. Subsequent scintigraphy and biopsy suggested follicular neoplasia and the patient underwent thyroidectomy, but cytology was benign.

As per additional information submitted on 10/15/15, a re-examination of the subject's lung biopsy sample (b) (6) noted that the histological picture indicated **cryptogenic fibrosing alveolitis, with obliterative arteriopathy**. The update noted that she was treated with IV methylprednisolone 40 mg/day Days 423 to 431 and orally, 8 mg/day on Days 432-436.

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*The patient developed two immune mediated conditions: nodular goiter and idiopathic pulmonary fibrosis (cryptogenic alveolitis). The narrative reports that pulmonary fibrosis resolved 3 days after the lung biopsy which was done 4 months after drug discontinuation. In my opinion is unlikely that cryptogenic alveolitis would resolve in 3 days. The patient profile shows th at she received systemic corticosteroids. In a fu IND safety report submitted in October 2015 (2013bi037098), the reported noted that the pt had 2-3 prior episodes of possible non-serious bronchopneumonia diagnosed radiographically. She was admitted 12 months after onset of pulmonary inflammation. Bx showed granulomatous pneumonitis. At the time of bx she had received 11 months of DAC in study 203 and had been off therapy for 4 months. She showed gradual improvement WITHOUT anti-inflammatory treatment. The event was considered resolved 7 months after stopping DAC HYP. **There are several inconsistencies in the narrative and 15-day safety reports for this case on important issues such as the duration of the event and whether the patient received corticosteroid treatment or not.***

To return to SAE section click 8.4.2.

13.3.16 Skin and Subcutaneous Tissue disorders SOC. Tables, listings and narratives of SAE and DROPOUTS

13.13.16.1 Skin and SC tissues disorders analyses by HLGT, HLT and PT in study 301

System Organ Class	High-Level Group Term	High-Level Term	Preferred Term	DME	Signal At					Treatment:		Control:		Relative Risk*	Cont/Contr
					Signal	SOC	HLGT	HLT	PT	150 mg DAC HYP and Avonex placebo N=919		30 ug Avonex and DAC HYP placebo N=922			
										Subject Count	%	Subject Count	%		
Skin and subcutaneous tissue disorders										343	37.3	176	19.1	2.0	
Skin and subcutaneous tissue disorders	Angioedema and urticaria	Angioedemas	Angioedema							3	0.3	0	0.0	7.0	*
Skin and subcutaneous tissue disorders	Epidermal and dermal conditions	Bullous conditions	Dermatitis bullous							2	0.2	0	0.0	5.0	*
Skin and subcutaneous tissue disorders	Epidermal and dermal conditions	Dermatitis and eczema	Eczema asteatotic							2	0.2	0	0.0	5.0	*
Skin and subcutaneous tissue disorders	Epidermal and dermal conditions	Dermatitis and eczema	Eczema nummular							7	0.8	0	0.0	15.0	*
Skin and subcutaneous tissue disorders	Epidermal and dermal conditions	Dermatitis and eczema	Neurodermatitis							2	0.2	0	0.0	5.0	*
Skin and subcutaneous tissue disorders	Epidermal and dermal conditions	Dermatitis and eczema	Seborrhoeic dermatitis							27	2.9	4	0.4	6.8	
Skin and subcutaneous tissue disorders	Epidermal and dermal conditions	Erythemas	Rash erythematous							3	0.3	0	0.0	7.0	*
Skin and subcutaneous tissue disorders	Epidermal and dermal conditions	Exfoliative conditions	Exfoliative rash							20	2.2	4	0.4	5.0	
Skin and subcutaneous tissue disorders	Epidermal and dermal conditions	Exfoliative conditions	Exfoliative rash							8	0.9	1	0.1	8.0	
Skin and subcutaneous tissue disorders	Epidermal and dermal conditions	Papulosquamous conditions	Erythema annulare							2	0.2	0	0.0	5.0	*
Skin and subcutaneous tissue disorders	Epidermal and dermal conditions	Papulosquamous conditions	Pityriasis rosea							5	0.5	1	0.1	5.0	
Skin and subcutaneous tissue disorders	Epidermal and dermal conditions	Psoriatic conditions	Psoriasis							18	2.0	3	0.3	6.0	
Skin and subcutaneous tissue disorders	Epidermal and dermal conditions	Psoriatic conditions	Pustular psoriasis							14	1.5	2	0.2	7.0	
Skin and subcutaneous tissue disorders	Epidermal and dermal conditions	Psoriatic conditions	Pustular psoriasis							3	0.3	0	0.0	7.0	*
Skin and subcutaneous tissue disorders	Skin and subcutaneous tissue disorders	Panniculitides	Panniculitides							2	0.2	0	0.0	5.0	*
Skin and subcutaneous tissue disorders	Skin and subcutaneous tissue disorders	Panniculitides	Erythema nodosum							2	0.2	0	0.0	5.0	*

PT with RR at least 5 fold on DAC150 as compared to IFNb1a (extracted from JumpSTART analyses conducted with MedDRA at a Glance).

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13.13.16.2 Serious AE Skin and SC tissues disorders analyses by HLGT, HLT and PT in study 301

System Organ Class	High-Level Group Term	High-Level Term	Preferred Term	DME	Signal At					Treatment:		Control:		Risk Difference	Relative Risk*	Cont Corr
					Signal	SOC	HLGT	HLT	PT	150 mg DAC HYP and Avonex placebo N=919		30 ug Avonex and DAC HYP placebo N=922				
										Subject Count	%	Subject Count	%			
Skin and subcutaneous tissue disorders	Angioedema and urticaria								2	0.2	0	0.0	0.2	5.0	*	
Skin and subcutaneous tissue disorders	Angioedema and urticaria	Angioedemas							2	0.2	0	0.0	0.2	5.0	*	
Skin and subcutaneous tissue disorders	Angioedema and urticaria	Angioedemas	Angioedema						2	0.2	0	0.0	0.2	5.0	*	
Skin and subcutaneous tissue disorders	Cornification and dystrophic skin disorders								1	0.1	0	0.0	0.1	3.0	*	
Skin and subcutaneous tissue disorders	Cornification and dystrophic skin disorders								1	0.1	0	0.0	0.1	3.0	*	
Skin and subcutaneous tissue disorders	Cornification and dystrophic skin disorders	Hyperkeratoses	Lichenoid keratosis						1	0.1	0	0.0	0.1	3.0	*	
Skin and subcutaneous tissue disorders	Cutaneous neoplasms benign								0	0.0	1	0.1	-0.1	0.0		
Skin and subcutaneous tissue disorders	Cutaneous neoplasms benign	Skin cysts and polyps							0	0.0	1	0.1	-0.1	0.0		
Skin and subcutaneous tissue disorders	Cutaneous neoplasms benign	Skin cysts and polyps	Dermal cyst						0	0.0	1	0.1	-0.1	0.0		
Skin and subcutaneous tissue disorders	Epidermal and dermal conditions								10	1.1	0	0.0	1.1	21.1	*	
Skin and subcutaneous tissue disorders	Epidermal and dermal conditions	Dermatitis and eczema							3	0.3	0	0.0	0.3	7.0	*	
Skin and subcutaneous tissue disorders	Epidermal and dermal conditions	Dermatitis and eczema	Dermatitis						3	0.3	0	0.0	0.3	7.0	*	
Skin and subcutaneous tissue disorders	Epidermal and dermal conditions	Dermatitis ascribed to specific agent							2	0.2	0	0.0	0.2	5.0	*	
Skin and subcutaneous tissue disorders	Epidermal and dermal conditions	Dermatitis ascribed to specific agent	Drug reaction with eosinophilia and skin manifestations						1	0.1	0	0.0	0.1	3.0	*	
Skin and subcutaneous tissue disorders	Epidermal and dermal conditions	Dermatitis ascribed to specific agent	Toxic skin eruption						1	0.1	0	0.0	0.1	3.0	*	
Skin and subcutaneous tissue disorders	Epidermal and dermal conditions	Papulosquamous conditions							1	0.1	0	0.0	0.1	3.0	*	
Skin and subcutaneous tissue disorders	Epidermal and dermal conditions	Papulosquamous conditions	Pityriasis rubra pilaris						1	0.1	0	0.0	0.1	3.0	*	
Skin and subcutaneous tissue disorders	Epidermal and dermal conditions	Psoriatic conditions							2	0.2	0	0.0	0.2	5.0	*	
Skin and subcutaneous tissue disorders	Epidermal and dermal conditions	Psoriatic conditions	Psoriasis						1	0.1	0	0.0	0.1	3.0	*	
Skin and subcutaneous tissue disorders	Epidermal and dermal conditions	Psoriatic conditions	Pustular psoriasis						1	0.1	0	0.0	0.1	3.0	*	
Skin and subcutaneous tissue disorders	Epidermal and dermal conditions	Rashes, eruptions and exanthems NEC							1	0.1	0	0.0	0.1	3.0	*	
Skin and subcutaneous tissue disorders	Epidermal and dermal conditions	Rashes, eruptions and exanthems NEC	Rash maculo-papular						1	0.1	0	0.0	0.1	3.0	*	
Skin and subcutaneous tissue disorders	Epidermal and dermal conditions	Skin injuries and mechanical dermatoses							1	0.1	0	0.0	0.1	3.0	*	
Skin and subcutaneous tissue disorders	Epidermal and dermal conditions	Skin injuries and mechanical dermatoses	Decubitus ulcer						1	0.1	0	0.0	0.1	3.0	*	
Skin and subcutaneous tissue disorders	Skin vascular abnormalities								1	0.1	0	0.0	0.1	3.0	*	
Skin and subcutaneous tissue disorders	Skin vascular abnormalities	Skin vasculitides							1	0.1	0	0.0	0.1	3.0	*	
Skin and subcutaneous tissue disorders	Skin vascular abnormalities	Skin vasculitides	Leukocytoclastic vasculitis						1	0.1	0	0.0	0.1	3.0	*	

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Selected narratives from this listing are included below. I believe that all events listed below are related to DAC HYP.

Study 201		
201/ 508-004	SAE DERMATITIS EXFOLIATIVE/ ALOPECIA	47 F. On DAC HYP 150. Onset on Day 214, “resolved Day 221.” Approx. 4 weeks after the 6 th dose she presented skin rash on neckline, armpits and groin area, treated with cetirizine and topical treatment. Interpreted as reaction to aspirin or cosmetics. She received two more doses of DAC. On (b) (6) she was hospitalized with erythrodermia and fever after 8 doses of DAC. Her last DAC dose was (b) (6) approx. 2 weeks before the event. No conc. meds. No allergies. She was treated with topical hydrocortisone, boric acid and discharged with condition improved but not fully resolved. On (b) (6) she began to experience alopecia . Derm exam showed fine flakes desquamation type on the body and many layers of crust on the head. Treatment included topical tacrolimus on face, prednisolone cream, topical salicylic acid, retinoids and emollients for the scalp. By (b) (6) the dermatologist stated that the symptoms had practically disappeared except for desquamation of the upper extremities. Dose and frequency of prednisone was reduced. Erythrodermia resolved with sequela of mild discoloration by July 2009. <i>The dataset states that no action was taken for the erythroderma, but the narrative says that drug was discontinued (because of alopecia). IT is unclear to me if alopecia resolved.</i>
201/ 751-016	SAE ERYTHEMA NODOSUM	46 M. On DAC HYP 300. Onset day 254, resolved by Day 402. Last dose of DAC HYP (dose #9) had been Day 225. Described as “panniculitis nodosa subacute migrans,” (“Syndrome of Vilanova-Pinol”). No conc. meds. Hx of chronic gastritis. No Hx of allergy. On Day 254 presented edema and erythema of right leg. Hospitalized with provisional diagnosis of erysipelatous inflammation. US of legs and abdomen was negative. Drug WD. Treated with prednisolone and antibiotics and also plasmapheresis . Biopsy of the node consistent with “nodular panniculitis”. Event was considered resolved after approximately 5 months with sequelae (sclerodermoid infiltration of the skin in “sock” distribution).
Study 301 (all on DAC HYP 150)		
301/ 441-021	SAE ANGIOEDEMA and urticaria	40 F. Onset Day 226, resolved Day 286. She had non serious AE of angioedema on Day 215, 3 weeks after the 8th dose of DAC. The event resolved on Day 225. Treatment included prednisolone . She received another DAC dose on Day 225. A <u>SAE</u> of face angioedema and urticaria was reported on Day 226. Patient was hospitalized with migrating erythematous-papulous plaques on trunk thighs and face consistent with urticaria. She also had non-productive cough, fever 39C and slight dyspnea with paroxysmal stabbing chest pains . She thought that she had “probably” been stung by an insect 24 hours prior. Angioedema and urticarial thought to be of viral etiology with rapid response to corticosteroids (oral prednisone). She was discharged after 2 days, continued treatment and entered study 303. She had intermittent mild eczema and was eventually WD after 28 doses of DAC because of a severe cutaneous allergy (coded as “allergic dermatitis”) in study 303 that did not resolve. <i>It is unclear if the episodes of angioedema were related to DAC HYP but she later developed allergic dermatitis, likely</i>

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		<i>related to DAC.</i>
301/ 552-014	SAE ANGIOEDEMA	47 F. Onset Day estimated to be 445, resolved Day 645. Most recent dose of DAC had been on Day 422. Concomitant meds: captopril, ibuprofen, thomapyrin. In February 2013, an event of lip swelling occurred 2 hours after administration of unspecified Chinese herbals, which improved with desloratadine treatment. On August 20, 2013, one hour after taking ibuprofen for headache she had edema of the face, lips, eyelids and neck. Post resolution of angioedema an allergist diagnosed “ chronic CMV infection of a high degree, ” ascariasis and NSAID intolerance. The patient continued treatment and completed the study. <i>If patient continued treatment without recurrence of angioedema, this is unlikely related to DAC. This patient later developed hypersensitivity pneumonitis in study 301. It is unclear why a diagnosis of CMV infection was made.</i>
301/ 152-004	SAE DERMATITIS and PSORIASIS	43 M, Onset Day 371. <i>Presented exfoliative erythrodermia and psoriasis. Drug WD. Required systemic corticosteroids and took several months to resolve after DAC discontinuation. See narrative after table.</i>
301/ 512-002	SAE DERMATITIS (toxic dermatitis)	27 F, Onset Day 171, widespread eczematous erythema and toxic dermatitis. Drug WD. Required systemic corticosteroids. Treated with plasmapheresis. Resolved 9 months after discontinuation of DAC. <i>See narrative after table.</i>
301/ 512-006	SAE DRESS	27 F. Onset Day 213, resolved day 337. After 4 doses of DAC. Drug WD. Patient had injection site erythema on Day 34 and 57. Toxic dermatitis diagnosed Day 94 to 213, severe, described as maculopapular rash covering >30% of body. DRESS was diagnosed Days 213-337. She also had eosinophilia and slight pancreatitis. Treated with prednisolone , antibiotics, fluconazole for vaginal and oral candida and plasmapheresis, starting on Day 222. DAC Antibody negative. <i>I disagree with the central dermatologist and believe that this case is consistent with DRESS (rash, eosinophilia, pancreatitis). It took several months to recover. Unclear how long continued on prednisone.</i>
301/ 512-011	SAE LEUKOCYTOCLAS TIC VASCULITIS	31 M. On Day 475 he developed petechiae of lower leg. Two weeks prior he had a mild “virosis”. Drug WD. On Day 477 a dermatologist noted diffuse maculopapular eruptions on arms and legs. ESR and CRP were mildly elevated. Treatment with prednisolone showed no improvement of the rash or joint and muscle pain. On Day 485 a biopsy showed necrotizing leukocytoclastic vasculitis with deeper vessel wall involvement. He underwent plasmapheresis x5 over two weeks, and the process improved considerably. Event was considered related to study drug and resolved on Day 500. <i>Unclear how long the patient required prednisone.</i>
301/ 745-001	SAE SAE LICHENOID	20 F. Onset Day 460, End Day 483. Had 3 episodes of MS relapse on Day 12, 196 and 686, treated with MP. Dark pigmentation over metacarpal area of hands on Day 421-457 (after 16 doses of DAC). Improved with antihistamines and mometasone. Generalized lichenoid keratosis was reported on Day 457 (after 17 doses of DAC; most recent dose on Day 449). Drug WD. The event became serious on Day 460, Hospitalized (b) (6)

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	KERATOSIS	(b) (6) for management of lichenoid keratosis. Maculopapular rash was found on upper arm, neck with redness and pruritus, later extended to chest, abdomen, thighs and back. Didn't involve the face. The event was associated with MS relapse. Treated with hydroxyzine, fexofenadine and methylprednisolone. Skin bx from right thigh performed; impression was subcorneal pustule with chronic dermatitis and vasculitis . He was treated with prednisolone . Labs showed leukocytosis (16,000) with 83% neutrophils. Event of lichenoid keratosis and MS were reported as resolved on Day 483. <i>I am not sure about the hyperpigmentation of MP joint area but the event of hyperkeratosis, chronic dermatitis and vasculitis is consistent with a DAC-induced reaction.</i>
301/ 147-002	SAE PITYRIASIS RUBRA PILARIS	36 F, from event lasted from Day 279 to Day 527. Occurred after 8 doses of DAC (Day 225). Drug WD. Associated with thickening and desquamation including palms and soles, with weeping sores because of staph superinfection; also alopecia. The pain was noted as worse on her hands and feet and included both ears. Labs results included a white blood cell (WBC) count of $21.7 \times 10^9/L$ (reference range 4.0×10^9 to $10.0 \times 10^9/L$) with elevated neutrophils. Required high dose prednisone for several months. The subject's scalp, face, eyelids, lips, and neck were patchy and "moth-eaten," and non-scarring alopecia on the central and parietal scalp with evidence of regrowth was observed. Methotrexate was added at some point. Glatiramer started as alternative MS medication. Event of pityriasis rubra resolved on Day 527. <i>Required systemic corticosteroid treatment and resolved with sequela after several months of discontinuing DAC.</i>
301/ 614-004	SAE PSORIASIS	50 M, Onset Day 507. Medical Hx of coronary artery disease, psoriasis (diagnosed 20 years earlier). At the start of the study the subject had only small plaques on the lower legs. A non-SAE of psoriasis was reported, after 12 doses of DAC. Concomitant meds at the time included allopurinol, fenofibrate and topical treatment for psoriasis. On day 507 he had exacerbation of psoriasis that did not improve for over 2 months. At that time transdermal fluocinolone was started. Four months after exacerbation started he was hospitalized for 5 days for planned treatment of psoriasis. He received selective ultraviolet phototherapy and the event resolved on Day 589.
301/ 600-004	SAE PUSTULAR PSORIASIS	55 M. Onset day 299, resolved Day 310. He presented a non-SAE of contact eczema on Day 116 of treatment, after 5 doses of DAC HYP (dose #5, Day 113). On Day 118 he presented papulopustular eruptions with peeling of the epidermis, mainly of the fingertips. One more dose of DAC was given (dose #6, Day 140), then drug was WD. A dermatologist diagnosed pustular contact dermatitis of the hands and feet. Skin Bx was unspecific. Patient was treated with topical and systemic corticosteroids (prednisone). Lesions resolved after 4 months. However, they reappeared once prednisone was tapered below 10 mg/day, with recurrence of new pustules. On Day 299, a SAE of pustular psoriasis was reported which ended on Day 310. He was subsequently withdrawn from the study. <i>I think all events are related to DAC. The SAE of pustular psoriasis was almost 5 months after stopping DAC, but still within the 6-month window of possible PD effects. Short follow up. It would have been informative have</i>

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		<i>additional follow up to be sure that pustulosis did not return.</i>
301/ 156-004	SAE RASH MACULO- PAPULAR	45 F, Onset Day 680. Hx of hypothyroidism, palpable inguinal node, joint pains. On Day 680 diffuse maculo-papular rash was reported (after 25 doses of DAC) on abdomen, extended to the back and extremities. Concom meds included amitriptyline, naproxen, levothyroxine, plantago ovata and hydroxyzine which she had been taken for several months. She was treated with prednisone for unclear duration. DAC was WD (last dose was on Day 673). Along with rash she presented lymphadenopathy , which started one month prior to the rash. The rash was considered resolved on Day 687 but the event of lymphadenopathy continued. She did have an inguinal node at entry to the study, it is unclear if she presented additional lymph nodes. And she was on hydroxyzine at time of the event, it is unclear why she was taking it if the event started on Day 680. <i>Although reported as resolved, it is unclear for how long prednisone treatment was required. Rash and lymphadenopathy but not enough for DRESS.</i>
301/ 537-017	SAE TOXIC SKIN ERUPTION	30 M. Onset day 611, resolved Day 634. On Day 604 (b) (6) rash was reported after 22 doses of DAC. The most recent dose was Day 589. No conc. meds were reported. He was treated with topicals and prednisolone with some improvement. DAC was WD. On Day 609 she had fever of 38.7C during the night and a severe rash which spread to arms, thighs, abdomen and chest. On Day 611 she was hospitalized with SAE of toxic skin eruption. The rash was highly inflammatory and spread all over the body limiting self-care and performance of activities of daily living . Some lesions had bluish discoloration and drying erosive areas of various sizes and shapes with isolated infiltrative lesions (4-6 cm diameter) on the face, neck arms and feet. Tests for hepatitis B and C, ova and parasite, HIV and fungus were negative. Hematology and chemistry labs were reportedly normal. Treatment included loratadine, diphenhydramine and mometasone. Skin lesions fully regressed and she was discharged from the hospital on (b) (6) (Day 634). <i>The patient had a serious skin reaction with fever, and spent almost a month in a hospital but improved after DAC discontinuation and systemic corticosteroids. It is unclear how long she needed corticosteroids. Unclear why she had Ova and parasite testing. Eosinophilia? Diarrhea?</i>
Study 202		
202/ 301-010	SAE DRUG ERUPTION (vesicles involving palms and soles) Atypical Pneumonia,	47 M. SAE on Day 253, after 7 doses of DAC (last dose was (b) (6)). Ended Day 422. Had received placebo in 201. He had a history of trigeminal neuralgia; conc. meds were beclomethasone inhalation, carbamazepine, citalopram, gabapentin. In (b) (6) he developed red itchy patches on his hands that progressed to forearms, face, neck, torso and feet. The erythematous scaling plaques had a “vesicular element on the palms and soles.” Event was diagnosed as dermatitis, treated with topical steroids and antibiotics. Drug WD at pt’s request. Rash considered resolved (b) (6) A week later, almost 3 months after the last dose of DAC, he was hospitalized with bilateral cellulitis and drug eruption and was treated with amoxicillin and MP. At that time had elevated

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	(ICU for 3 wks). DRESS?	WBC (19.1) and eosinophilia (0.9×10^9 ; normal range <0.4). A few days later he developed pneumonia and was admitted to the ICU with diagnosis of atypical pneumonia (CT scan showed ground glass changes consistent with pneumonitis or resolving consolidation from recent pneumonia. He also had small mediastinal lymph nodes, thought to be “likely reactive”. He was discharged from hospital after 3 weeks. The rash was improved but still suberythrodermic. Dermatologist treated him with prednisone 20 mg/day. Prednisone taper took long time because of persistent pyriasiform lesions that worsen with lower doses. (He was on prednisone 15 mg until (b) (6) two months after hospital discharge. Steroids finally finally discontinued (b) (6) (almost 10 months after last dose of DAC). He had rash, eosinophilia, atypical pneumonia, mediastinal lymphadenopathy. <i>Pneumonia “not resolved” as of the SUR. I believe this case is consistent with DRESS. A possible differential diagnosis is sarcoidosis.</i>
202/ 765-003	SAE URTICARIA/ thyroiditis, hepatitis, leukopenia colitis IPEX?	27 F. On DAC300. She had no relevant Hx at entry to 201. Developed non-SAE of nodular goiter and thyroiditis after 7 doses of DAC in 201. In 202 had SAE of acute generalized urticaria after a total of 20 doses of DAC300. Event of urticaria described as rash on arms, body and face, leading to hospitalization. Treatment included dexamethasone . Event considered resolved 12 days later. Investigator thought it was not related to drug, and treatment continued but additional events of gastroenterocolitis, ALT/AST elevation, drug-induced leukopenia, diffuse toxic goiter, thyrotoxicosis, and chronic hepatitis occurred after a total of 25 doses of DAC 300).
Study 203		
203/ 453-021	SAE URTICARIA Asthma Elevated liver enzymes	23 F. had presented atopic eczema and contact dermatitis in study 202. SAE of urticaria was on Day 6 and resolved by Day 10 of study 203 but continued as a non-serious AE til Day 35. Bronchial asthma on Day 6 to 76. Drug was interrupted after 2 doses in 203, but never restarted due to hepatic enzymes increased on Day 62-337. Concom meds: nimesulide, cetirizine, montelukast. <i>DRESS?</i>
203/ 453-014 *	SAE SEBORRHEIC DERMATITIS vs. PARAPSORIASIS	IND REPORT 2015BI055344 in August 2015. 49 F was hospitalized for suspected plaque parapsoriasis (pre-malignant lesion) after 6 ½ years of treatment with the study drug (b) (6) improved with topical corticosteroids. Report later amended to preferred term of seborrheic dermatitis. Patient had a prior episode of papular rash on the abdomen 2 years prior. Granulomatous changes were read as consistent with sarcoidosis but the final diagnosis was foreign body granuloma (at insulin application site) that resolved.
203/ 901/006	SAE SJS <i>In my opinion consistent with</i>	39 M. SJS reported by investigator. However, none of the dermatologists confirmed this diagnosis. He had multiple organ system involvement and diagnosed with <u>secondary immunodeficiency with autoimmune syndrome</u> with signs of skin and mucosa lesions. Treatment included IV dexamethasone and oral methylprednisolone. Symptoms resolved by Day 478. The subject withdraws from the study and

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	DRESS	there is no further follow up. See extended narrative after the table.
Study 303		
303/ 609-013	SAE GENERALIZ RASH	37 M. Moderate rash from Day 1071 to 1073. No action taken with drug. WD because of worsening SAE of lymphadenopathy. Peripheral edema with <u>exfoliative rash, pulmonary nodules and hilar lymphadenopathy</u> , suspected Drug Reaction with Eosinophilia and Systemic Symptoms. The patient received 33 doses of DAC in study 301 and 3 in study 303. On Day 1065 of treatment he developed exfoliative rash. He was hospitalized for 2 days, treated with dexamethasone and topical steroids and discharged home. Drug was discontinued. A skin biopsy done 2 weeks later showed chronic eczema. He received treatment for approximately 6 weeks. On Day 1160 (3 months later) hospitalized again for <u>peripheral edema and generalized eczema</u> , generalized lymphadenopathy (including hilar and hepatic areas) and suspected paraneoplastic syndrome. At that time he also had <u>anemia and lymphopenia</u> . He was treated with IV corticosteroids , furosemide, potassium and topical treatment. The aspirate showed “reactive irregularities”. Both the rash and lymphadenopathy resolved after several months. <i>The data are insufficient for a definitive diagnosis of DRESS, although I would not rule it out. In my opinion interstitial nodules along with hilar lymphadenopathy and other signs and symptoms are consistent with a clinical diagnosis of sarcoidosis.</i>
303/ 512-009	DRESS <i>Mild increase in ALT <2xULN accompanied by lip and face swelling, fever, eosinophilia</i>	47 M. Moderate intensity. On Day 96 of study 303. 2 weeks after 3rd dose of DAC (b) (6) Drug withdrawn. Resolved on Day 202. He had received IFNβ1a in 301. In 303, developed maculopapular rash initially moderate treated with topical treatment but got worse >30% BSA, highly inflammatory, led to withdrawal. On (b) (6) Punch bx: perifollicular lymphohistiocytic inflammation. Presence of fungal spores (pityrosporum). Individually identifiable single eosinophils, no deep inflammatory infiltrates. “Toxicodermatitis of an eczematous subacute type with elements of moderate eosinophilia”. On (b) (6) fever, eosinophilia (25%). Treated with adrenaline and betamethasone. Treated with plasmapheresis x5, day 103 to 133, rash initially improved but then came back. He was treated with prednisone 60 mg/day. In (b) (6) ALT was 71 U/L (6-43). Eosinophilia (9.4% [0-6.8%]). Rash resolved (b) (6) <i>Serious rash, face edema, ALT elevation, eosinophilia, highly suggestive of DRESS. Took 3 months to resolve.</i>
303/ 659-116*	Cutaneous sarcoidosis	35 F IND safety report (2015BI066849) Cutaneous sarcoidosis 3 years into treatment with DAC HYP (initially reported as Granulomatous dermatitis). See narrative below

Extended narratives of selected cases

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203/901-006. 39 M. On (b) (6) study day 336 of DAC HYP treatment was admitted to the hospital with itching of the eyelids, conjunctivitis, bleeding of gums and lips, dry mouth, skin peeling of the lips and weight loss of 10 kg over the last 3 months, reported as Stevens-Johnson syndrome (SJS). This occurred after 26 doses of DAC HYP (13 doses in 203). Drug was discontinued. There was moderate desquamation of skin on the superficial layers of the hands, face, lips eyelids and oral mucosa no full thickness skin loss. He had no fever. He was also diagnosed with bilateral retinal angiopathy. Labs showed WBC of $20,000 \times 10^9/L$, with 25% eosinophils evidence of tongue edema. He was treated with IV dexamethasone, and electrolytes and discharged with "improved condition". Two weeks later he was readmitted to the hospital, Allergy department, because of increased bleeding of the gums and swelling of lower legs, associated with rash on the arms and peeling of the skin on the arms and fingers. He was in poor overall condition with trophic disorders on the palms, scaling, punctuate rash on the lower legs, oral mucosal ulcers. There were enlarged peripheral lymph nodes. On (b) (6) a CT showed fatty liver and cronic cholecysto-pancreatitis. An US of the tyroid showed goiter. He had "troubled of tongue and inferior lips" and feeling of swelling of the tongue. A dermatologist thought the clinical picture was consistent with some vitamin deficiency, perhaps Vit B12. A chest XRay showed emphysema and signs of pulmonary heart disease; and echocardiogram showed MVP with pronounced regurgitation and MV insufficiency, and reduced contractility of the left ventricle with "post myocardic fibrosis." (*The patient already had a history of MVP and rheumatic heart disease, it is unclear if there is worsening of prior pathology or new/ superimposed heart disease*). Viral testing was consistent with prior infection with HSV 1 and 2 and CMV, but no IgM. ANA was positive (no titer provided. An hematologist diagnosed mild anemia and a neutrophilic leukemoid reaction. The myelogram performed in (b) (6) showed blasts 1%, plasmocytes 3%, and binuclear plasma cells. Treatment included IV dexamethasone and oral methylprednisolone. He was diagnosed with improved condition. The final diagnosis was "**Secondary immunodeficiency with autoimmune syndrome,**" On 02 January 2013 (Study Day 478), the subject had no cutaneous symptoms, recovered his loss of sense of taste and gained weight; the event was considered resolved. The subject withdrew from the study. *In my opinion this cases is consistent with DRESS.*

A graphic presentation of AE in this patient is presented below .

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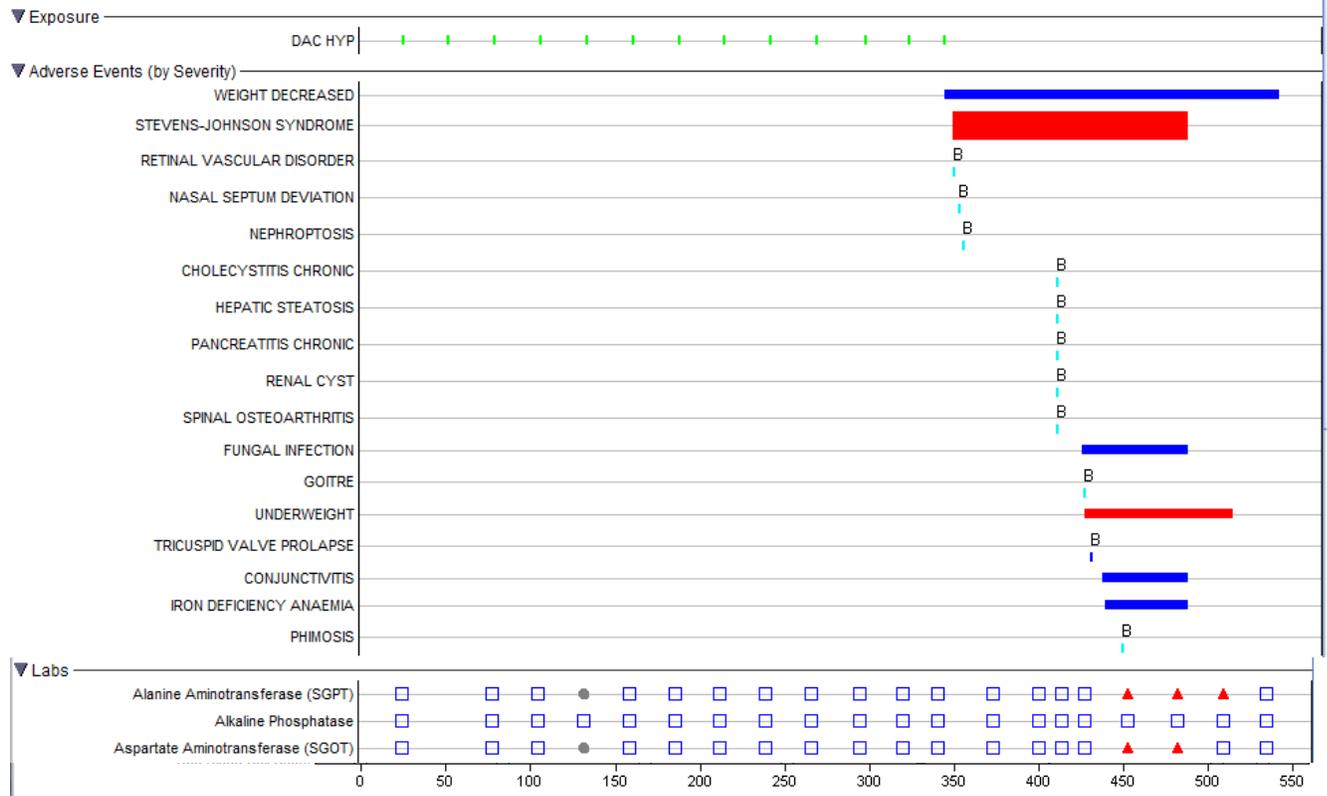
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Empirica Study Data Montage Graph for patient 203/901-006

Subject: 205MS203/901-006 - Age: 41 - Sex: M - Race: WHITE
Study Arm: 150 mg DAC HYP



302-659-116* 35 F. IND safety report (2015BI066849) **Cutaneous sarcoidosis** (initially reported as Granulomatous dermatitis to foreign body). No hx of allergy. First dose of DAC was May 21, 2012. Event of cutaneous sarcoidosis was reported May 18, 2015 (3 years into treatment, unknown number of doses). Most recent dose prior to event was Jan 29, 2015. On (b) (6) serum angiotensin converting enzyme activity (SACE) test was performed with a result of 91.2 U/L (normal range: 20.2-70.0) and along with the skin biopsy the diagnosis changed to cutaneous sarcoidosis. Chest x-ray and eye exam did not show systemic involvement. Treatment included prednisone and topical betamethasone, salicylic acid and urea. Daclizumab was discontinued. A skin biopsy (b) (6) was consistent with chronic granulomatous dermatitis in reaction to foreign body or sarcoidosis. As per fu information submitted on 9/25/15, chest CT, PFT, TB testing and abdominal US, did not show evidence of sarcoid involvement. The patient started treatment with prednisone 30 mg day on April 18, 2015 and the skin reaction was noted to improve by April 24, 2015. *The skin lesion resolved as of September 15, 2015 but the continued on low dose corticosteroid treatment until January 2016, when the event was considered to be fully resolved while off prednisone.*

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Short narratives of selected patients with NON SERIOUS AE leading to DRUG WITHDRAWAL in the Skin and SC tissues SOC.

Study 301	
301/ 101-002	39 F. Psoriasis of severe intensity was reported on Day977 (September 2013). Last dose of DAC had been on Day 954. She had Hx of allergic reaction to Demerol, seasonal allergies, keratosis pilaris. On day 516 of study 301 after 19 doses of DAC presented alopecia of moderate intensity. Drug was later discontinued because of psoriasis, after 35 doses of DAC. She was treated with hydrocortisone, desonide, flocinonide, clobetasol and cyclosporine, among other meds. She had blisters on her fingers and palms for at least 2 months prior to the diagnosis of psoriasis. A dermatologist noted that there was mild fissuring, scaling and xerosis of both hands and fingers. Erythematous, nummular, scaly papules and plaques were observed. According to the dermatologist, the rash was secondary to an atopic diathesis and xerosis. When prednisone treatment was discontinued the rash reappeared. Biopsy of the lesions showed spongiotic and psoriasiform dermatitis. She improved with cyclosporine treatment but rash reappeared with treatment was stopped. The patient withdrew from the study and the investigator eventually considered the event resolved in Jan 2014, 9 months after stopping DAC HYP.
301/ 115-001	52 F, Hx of seasonal allergies, thyroid nodules. Developed non-serious postauricular seborrheic dermatitis, followed by skin erosion (bilateral hands/fingers eroded patches), rash erythematous, exfoliative rash (erythematous, scaly patches) after 10 doses of DAC HYP. Started around Day 240, and resolved around Day472. Drug was discontinued because of the erythematous rash. The palmar surface and fingers had scattered pink, scaly, eroded patches with deep-seated microvesicles and fissures at the fingertips . A punch biopsy of the left thumb revealed a vesicular dermatitis consistent with dyshidrotic eczema. Treated with clobetasol, terbinafine, topical antibiotics, clobetasol, prednisone, hydrocortisone and cephalixin.
301/ 186-003	23 F. HIVES, ALLERGIC REACTION, urticaria. Moderate intensity. On Day 156, WD After 6 doses. Patient presented injection site erythema, injection site mass, pruritus and injection site reaction, along with urticaria, since the first dose. Did not resolve.
301/ 307-002	50 F. RASH of moderate intensity On Day 172, WD After 7 doses of DAC. Resolved after 1 month
301/ 310-002	42 F GENERALISED MACULOPAPULAR RASH of moderate intensity. Started on Day 166, WD After 8 doses of DAC (May 2012). He did have a history of minor psoriasis (both elbows). Generalized rash first appeared after 6 doses (face, neck head, groin, trunk, back arms hands legs, feet, >30% of BSA). At that time he was taking amoxicillin. Last dose of DAC was on day 167. Treated with dermatological preparations, cetirizine, prednisolone . Rash eventually improved with phototherapy , (b) (6). The investigator thought that the maculopapular rash was related to amoxicillin. <i>In my opinion worsening psoriasis was related to DAC HYP.</i>

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301/ 412-002	23 F. Diffuse maculopapular rash of mild intensity After 18 doses. Concom med was an oral contraceptive. Rash was treated with methylprednisolone and prednisolone. The event resolved after 10 days.
301/ 477-006	37 M developed erythrodermic psoriasis on Day 130, after 5 doses of DAC HYP. Past Hx of erythema nodoso, spondylitis, uveitis. On Day 130 he developed erythrodermic psoriasis, classified as <u>non serious</u> . Concom meds included mirtazapine, sulfasalazine and citalopram. Last dose of DAC was in (b) (6) (Day 144). He was treated with deflazacort and petrolatum salicylicum. A few days later the lesions appear to be impetiginized, with exudative eczema on both feet . The rash was highly inflammatory. The event improved after plasmapheresis. However, two weeks later he had generalized pruritic erythema all over his body compatible with psoriasis like eczema versus occult psoriasis. Lesions continue to worsen, including scalp (moderate hair loss) and nails. As of November 2011 the event was unresolved. The patient was <u>withdrawn from the study</u> . <i>The patient seems to have had a seronegative spondyloarthropathy, and developed psoriasis while on treatment with DAC. There is no end date for this event.</i>
301/ 600-004	55 M, developed contact eczema of moderate intensity on Day 116, after 6 doses of DAC. It took 6 months to resolve. Patient also developed SAE of pustular psoriasis not resolved at time of last follow up.
301/ 606-019	49 F, developed erythroderma coded as exfoliative dermatitis of severe intensity 642 days into treatment after 23 doses of DAC. It took 277 days to resolve. Skin biopsy submitted (b) (6) as along with other skin biopsies showed that this patient had vasculitis . The patient had non-SAEs of dermatitis allergic, nummular eczema and macular rash prior to the diagnosis of vasculitis. A non-serious AE of Vasculitis was reported on Day 644. Concurrently, a non-serious but severe event of exfoliative dermatitis was also reported, along with elevated ALT and AST . She had received naproxen throughout the study and clarithromycin. Labs approx. one month after dx of vasculitis labs showed low neutrophil count, elevated lymph count, metamyelocyte present (abnormal) and low TSH. Renal function was normal. Event was treated with methylprednisolone , hydrocortisone and fluticasone propionate. Vasculitis resolved on day 647, exfoliative dermatitis resolved on Day 923 (280 days duration).
301/ 620-004	41 M, developed maculopapular exanthema on face and extremities of moderate intensity, exfoliative rash and desquamation over the head, on Day 422. Required treatment with hydrocortisone and prednisone . Withdrawn after 16 doses of DAC, It took approx. 3 months to resolve.
301/ 663-010	29 F, rash of mild intensity on Day 450 of study 301. Drug WD after 18 doses of DAC. It lasted approx. 3 months. As per Empirica Study: ALT elevation noted 2 days earlier (<2 xULN on Day 448) but continued to increase with peak 5x ULN on Day 590. Still at 3xULN at last visit Day 686. Patient also had arthralgia all along since the first dose of DAC.
301/	43 F, psoriasis vulgaris of moderate intensity on Day 557, preceded by contact dermatitis. <i>Hperthyroidism</i>

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666-007	<i>diagnosed on Day 551, not resolved. Drug WD after 20 doses of DAC. It resolved after 178 days, by Day 735. As per the concomitant medications datasets this patient underwent several tests, including skin biopsy and fungal cultures for evaluation of AGEP “after treatment stopped”. (b) (6) (day 559) and (b) (6) (Day 734). Therefore cutaneous reaction was not resolved.</i>
Study 203	
203/ 301-008	41 M, RASH MACULO-PAPULAR on day 430. WD After 15 doses of DAC. Received placebo in 201; Dac 150 in 202 and 203. Did not resolve
202/ 453-015	36 F, URTICARIA CHRONIC, mild, on day 1011, WD after 39 doses of DAC. Received placebo in 201; DAC 300 in 202 and 203. Resolved after one year.
458-003	39 F, Moderate DERMATITIS ALLERGIC started on Day 394. WD after 34 doses of DAC. Received placebo in 201; DAC 150 in 202 and 203. No end date for this event. Not resolved.
501-019	53 F, RASH MACULO-PAPULAR on Day 441. WD after 16 doses of DAC. Received placebo in 201 and DAC 300 in 202/203. Not resolved.
769-001	39 F, PHOTOSENSITIVITY REACTION of moderate intensity on Day 987. WD after 34 doses of DAC. Resolved after 5 months.
Study 302	
408-103	38 F, Severe Dermatitis allergic (generalized toxoallergic rash) reported on Day 651. WD after 19 doses of DAC 150 (received DAC 150 followed by washout and DAC 150). (HOWEVER, as per JREVIEW PP event presented since first dose, along with dermatitis atopic, allergic cough, hypersensitivity, treated with topical and systemic corticosteroids) Not resolved.
408-104	53 F, Severe Drug eruption (daclizumab rash) on Day 98. WD after 5 doses of DAC 150 (received DAC 150 followed by washout and DAC 150). As per JR PP also had severe alopecia. Not resolved.

To go back to SAE of SKIN disorders click 8.4.3.

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Table 13.3.16.2 Skin and SC tissues disorders analyses by HLGT, HLT and PT in study 301

System Organ Class	High-Level Group Term	High-Level Term	Preferred Term	DME	Signal At					Treatment: 150 mg DAC HYP and Avonex placebo N=919		Control: 30 ug Avonex and DAC HYP placebo N=922		Relative Risk*	Cont Corr
					Signal	SOC	HLGT	HLT	PT	Subject Count	%	Subject Count	%		
Skin and subcutaneous tissue disorders										343	37.3	176	19.1	2.0	
Skin and subcutaneous tissue disorders	Anqioedema and urticaria	Anqioedemas	Anqioedema							3	0.3	0	0.0	7.0	*
Skin and subcutaneous tissue disorders	Epidermal and dermal conditions	Bullous conditions	Dermatitis bullous							2	0.2	0	0.0	5.0	*
Skin and subcutaneous tissue disorders	Epidermal and dermal conditions	Dermatitis and eczema	Eczema asteatotic							2	0.2	0	0.0	5.0	*
Skin and subcutaneous tissue disorders	Epidermal and dermal conditions	Dermatitis and eczema	Eczema nummular							7	0.8	0	0.0	15.0	*
Skin and subcutaneous tissue disorders	Epidermal and dermal conditions	Dermatitis and eczema	Neurodermatitis							2	0.2	0	0.0	5.0	*
Skin and subcutaneous tissue disorders	Epidermal and dermal conditions	Dermatitis and eczema	Seborrhoeic dermatitis							27	2.9	4	0.4	6.8	
Skin and subcutaneous tissue disorders	Epidermal and dermal conditions	Erythemas	Rash erythematous							3	0.3	0	0.0	7.0	*
Skin and subcutaneous tissue disorders	Epidermal and dermal conditions	Exfoliative conditions								20	2.2	4	0.4	5.0	
Skin and subcutaneous tissue disorders	Epidermal and dermal conditions	Exfoliative conditions	Exfoliative rash							8	0.9	1	0.1	8.0	
Skin and subcutaneous tissue disorders	Epidermal and dermal conditions	Papulosquamous conditions	Erythema annulare							2	0.2	0	0.0	5.0	*
Skin and subcutaneous tissue disorders	Epidermal and dermal conditions	Papulosquamous conditions	Pityriasis rosea							5	0.5	1	0.1	5.0	
Skin and subcutaneous tissue disorders	Epidermal and dermal conditions	Psoriatic conditions								18	2.0	3	0.3	6.0	
Skin and subcutaneous tissue disorders	Epidermal and dermal conditions	Psoriatic conditions	Psoriasis							14	1.5	2	0.2	7.0	
Skin and subcutaneous tissue disorders	Epidermal and dermal conditions	Psoriatic conditions	Pustular psoriasis							3	0.3	0	0.0	7.0	*
Skin and subcutaneous tissue disorders	Skin and subcutaneous tissue disorders	Panniculitides								2	0.2	0	0.0	5.0	*
Skin and subcutaneous tissue disorders	Skin and subcutaneous tissue disorders	Panniculitides	Erythema nodosum							2	0.2	0	0.0	5.0	*

PT with RR at least 5 fold on DAC150 as compared to IFNβ1a (extracted from JumpSTART analyses conducted with MedDRA at a Glance)

To go back to All AE of Skin reactions click 8.4.4.

13.3.17 LAB RESULTS and VITAL SIGNS. Summary results and TABLES not included in body of the review.

LABORATORY ANALYSES

As per the CSR, in study 201, by week 44 there was a small decrease in mean and median WBC % in both DAC 150 and 300 groups (approximately -1%, without dose response) but by week 52, there was a small increase (3.7%) for DAC HYP 150 and a small decrease (-0.6%) for DAC HYP 300 (Source: Table 160, Study 201 CSR). Mean total lymphocyte counts showed a slight decline on DAC HYP groups as compared to placebo at week 52 with a suggestion of a dose response (4% decline from baseline in the DAC HYP 150 mg group and a 6% decline from baseline in the DAC HYP 300 mg group compared to a 3% decrease from baseline in the placebo group). This decline was driven by a decrease in both T and B cells.

- For CD4+ Tcells, there was a 7% and 9% decline from baseline in the DAC HYP 150 and 300 mg groups, respectively, as compared to a 3% increase from baseline in the placebo group. 48 subjects in the placebo group (24%), 52 subjects in the DAC HYP 150 mg group (25%), and 88 subjects in the DAC HYP 300 mg group (43%) met the criterion of a CD4+T cell count < 400 /L. For CD4+ T-cell counts <200 cells/L, 3 subjects in the placebo group (1%), 4 subjects in the DAC HYP 150 mg group (2%), and 8 subjects in the DAC HYP 300 mg group (4%) met the criterion.
- For CD8+ Tcells, there was a decline of 9% and 10% from baseline in the DAC HYP 150 and 300 groups, as compared to an increase of 3% for placebo. (the CD4/CD8 ratio was unchanged)
- For B cell counts, there was a decline from baseline of 4% and 11% in the DAC HYP 150 and 300 respectively, as compared to a 13% increase for placebo.

There was no apparent relationship between lymphocyte counts, particularly CD4+T cell counts and infections. (Source: Tables 160, 164, 124, 126, 127 and 128 of study 201 CSR, data not shown).

- NK cells counts were higher in the DAC HYP groups at week 52 (48% and 50% increase from baseline in the DAC HYP 150 and 300, respectively, as compared to 3% increase on placebo (Source Table 131, study 201 CSR). The applicant states that these are CD56^{bright} NK cells, induced by DAC HYP.

In study 301 mean changes from baseline in total WBC: similar in both groups (-4% on IFN and -3% on DAC HYP at week 144 (source, Study 301 CSR). Mean changes from baseline in lymphocyte count: At week 48, with approx. 800 patients per group, there was 2% decrease with IFN and -2.7% on DAC. At week 144 (approx. 240 pts per arm) the decrease was 0.8% for IFN and -8.7% with DAC 150, confirming that it causes mild lymphopenia. Also mild increase in segmented neutrophils at week 144 (-4.6% on IFN and 2% increase on DAC HYP).

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In the outlier analysis, a slightly greater number of patients had at least one decreased lymphocyte count measurement during study 201 (8%, 9% and 11% in the placebo DAC 150 and 300 groups respectively) but no patient had a decrease greater than 50% in any group.

Study 201, post baseline abnormalities, WBC and lymphocytes

Source: Table 175, study 201 CSR

Post baseline abnormalities WBC and Lymphocytes, study 301

L

Source table 264 Study 301 CSR.

Shift analyses of WBC parameters in 201 showed more frequent shifts from baseline to low than from baseline to high for lymphocytes counts. For neutrophils, shifts to high values occurred at higher frequencies for DAC HYP groups as compared to placebo (consistent with a higher incidence of infections). Shift analyses of WBC in 301 showed a slightly higher percentage of subjects with shifts from baseline to low values for WBC, lymphocytes and

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neutrophils for IFN as compared to DAC HYP (20% vs. 16% for WBC count, 15% vs.13% for lymphocyte count, and 21% vs.15% for neutrophil count, respectively). In the total DAC HYP experience, consistent with the findings in 301, the percentage of subjects with shifts from baseline to low or high values was similar for WBC. For lymphocytes, shifts from baseline to low were more common than shifts to high, with the opposite pattern for neutrophils.

Post baseline HB and platelet abnormalities in study 201

Source: Table 175, study 201 CSR.

Study 301. Clinically significant abnormalities in study 301

Neut:

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Plate

Source: Table 265, 301

Similar % of patients had significant hematology lab abnormalities in both treatment groups in study 301.

CD4 counts, study 301

<50 cells/mm³

NOTE: Number of patients
(a) For each treatment group

Source: Table 266 study 301 CSR.

7-9% had CD4 <400 at baseline. Slightly higher had CD4 <400 at some point during study was slightly higher with DAC150 as compared to IFNβ1a (22% vs. 17%, respectively). The percentage change in CD8 counts looked similar in both groups (data not shown).

In terms of NCI CTCAE hematologic abnormalities, there were 4 subjects (<1%) with low WBC Grade 3 toxicity, 19 (<1%) with low lymphocyte Grade 3 toxicity, 14 (<1%) with neutrophil Grade 3 abnormalities and 2 with Grade 4 neutrophil count abnormalities.

Table 127 of the SUR (“Listing of subjects with a NCI CTCAE grade ≥2 for selected hematology parameters”) provides relevant information but lists the patients by their dummy ID, not by the patient ID. In response to a DNP request for information, on February 1, 2016, the applicant submitted listings of patients with NCI CTCAE ≥3 using the unique patient ID, for all hematologic abnormalities, along with AE that may have occurred at the time of the abnormality. Review of these data did not identify any patient who had not been previously identified.

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Table. Actual values for creatinine over time, Total DAC HYP database.

DAC HYP Bas
n
Mean

Week 120
n
Mean
SD

Week 192
n
Mean
SD

Week 264
n
Mean
SD

From Table 131 of the SUR.

To go back to lab findings click here [8.4.5](#).

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13.3.18 UNRESOLVED AE AS OF THE SUR

As per the ISS AE datasets, at the time of the SUR, which had a cut-off date of November 2014, 1887 patients had at least one AE among 2236 in the Total DAC HYP. Of those, 710 were either serious or led to study withdrawal. Of the 1887, 1041 pts had at least one event that had not resolved, and 1811 patients had AE with no end date. Of the 1887, 1129 had at least one AE with no end date (1129/1887: roughly 60% of all AEs in the dataset). Of those with no end date, some were Not Resolved, and some had an unknown outcome.

Of the 1129 pts with AE and no end date, 46 had a SAE, 96 had an AE that led to drug withdrawal and 89 had both and a SAE and/or an AE that led to withdrawal. Overall, there were 127 with a SAE or an event leading to WD but no end date.

On August 25, 2015, the DNP asked the applicant to provide a follow up of all cases with serious AEs or AE that led to study drug withdrawal whose outcome was listed as “not resolved” in the Safety Update Report AE datasets.

On September 28, 2015, the applicant submitted a response but rather than providing a short narrative of what happened to each of these patients, they provided two separate listings with updated end of event dates, “as provided by the site.”²⁵ A few cases included a clarification that the data had been “entered by statistician.”

At that time, 51 patients had SAE or AE causing drug withdrawal that had not resolved or had no follow up data (51/710 = 7% of all patients with SAE or causing WD). For those with an end date (and considered “resolved”), there was no information whether the event had resolved with sequela or whether treatment was still required for that event. Moreover, a subsequent IND report could show that an event reported as resolved was in fact not resolved.

The findings related to events with no end date in the 9/28/15 response are summarized below. These listings seem to have been prepared by two different people. The one for SAE focuses on events that were not resolved as of the SUR; the one for AE leading to withdrawal focuses on patients with no end date as of the SUR.

Overall it appears that approximately 50 patients of the 710 with SAE or AE leading to drug WD as of the SUR (approximately 7%), still had events that were unresolved or with an unknown outcome as of September 2015.

²⁵ The intent of the FDA request was to learn whether events that were unresolved at the time of the SUR, had resolved 10 months later. On 9/24/15 the applicant submitted two unreadable, non-searchable pdf files, one for SAE and one for AE leading to WD. Upon request, on 9/28/15, the applicant submitted Excel files.

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Current status of patients with SAE and non-SAE leading to drug withdrawal that were not resolved at time of the SUR, as per listings submitted on 9/28/15 in response to FDA request.

	SAE	Non-SAE leading to drug WD
Nov 2014 (SUR cut-off)	46 not resolved	71 no end date
Sept 2015 response (current status)	20 not resolved Queried 11 SAE improving 3 SAE ongoing 1 SAE stable 4 SAE unresolved, unknown 1	31 no end date Ongoing 11 Unknown 7 Lost to FU 7 Not available 5 Uncertain 1

SUR submitted 2/28/2015, cut-off date for analyses, November 2014. End date of event provided by site. Analysis done by MO by hand from excel files.

Patients with SAE or AE leading to withdrawal that were not resolved or had no follow up data as of September 2015 are listed below.

13.3.19 Phase 1 studies of DAC HYP and studies with other daclizumab formulations

- **Safety of DAC HYP in phase 1 studies**

Across the four Phase 1 studies (DAC-1015, DAC-1014, DAC-1018 and 205HV102), a total of 127 Healthy volunteers were exposed to DAC HYP, 24 of whom received more than 1 dose and 25 of whom received placebo. Doses of DAC HYP ranged from 50 mg to 300 mg SC and 100 to 400 mg intravenously. In these studies, most subjects in the DAC HYP and placebo groups experienced at least 1 AE. The most frequently reported AEs in the Phase 1 studies were headache, upper respiratory tract infection, injection site pain, oropharyngeal pain, nasopharyngitis, dermatitis, and rash. Overall, 6 serious adverse events (SAEs) were reported in 5 DAC HYP-treated subjects. Three of these SAEs (staphylococcal bacteremia, viral pneumonia, and mesenteric adenitis) were assessed as related to DAC HYP. The SAEs of motor vehicle accident, appendicitis, and bibasilar atelectasis were assessed as not related to study treatment. There were no deaths or dose-limiting toxicities. The most common cutaneous events were dermatitis and rash. There was one episode of exfoliative dermatitis in Study DAC-1015 in a subject who developed a SAE due to complications by bacteremia (*similar to the patient who died in study 201*). The safety in the phase 1 studies is summarized below.

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Table 13.3.19.1 Summary of safety results in phase 1 studies with DAC HYP

Study Route	N	Dosing/duration	Comment
DAC-1015 single dose	34 SC	Placebo (n=11), DAC HYP 50 (n=7) DAC HYP 150 (n=8) DAC HYP 300 (n=8)	Common AE (>1): Up Resp Infection, headache, site pain, nausea, pharyngitis. SAE: dermatologist exfoliative with staph bacteremia following dyshidrosis treated with CS (on DAC 50).
DAC-1014 Q 2wks x 9 doses	32 SC	Placebo (n=8) DAC HYP 200 (n=12) DAC HYP 200x1 + DAC HYP 100 x8 (n=12)	Common AE: injection site reaction (including pbo) SAE: viral pneumonia and mesenteric adenitis Cutaneous events: 42% of DAC, 0% placebo Decreased CD4 lymphs by 20 to 25% in DAC HYP subjects as compared to placebo. No clear association with AE of infection.
DAC-1018 Single dose	31 IV	Placebo (n=7) DAC HYP 200 (n=12) DAC HYP 400 (n=12)	Common AE Headache, upper resp infection, cough pharyngeal pain, dermatitis. SAE: appendicitis and atelectasis (in DAC400)
205HV102 Single dose	56 SC	DAC HYP 75 (n= 28) or DAC HYP 150 (n=28), half Japanese and half Caucasian.	Common AE: nasopharyngitis, cough, headache, influenza like illness and rash. 1 severe AE of tonsillitis. Incidence of infections and cutaneous events was similar across groups. No SAE.

Source: Applicant’s Summary of Clinical Safety, text, original submission. N=total number of patients.

Overall, there were no clinically significant trends in hematology or blood chemistries across the four phase 1 studies

- **Safety in studies conducted with other DAC formulations (Nutley and Penzberg).**

DAC Nutley (ZENEPAX) was once approved for prophylaxis of acute rejection in patients undergoing renal transplant before being withdrawn from the market. The label for ZENEPAX includes information from premarketing trials which were done in a background of cyclosporine and corticosteroids and does not directly reflect the safety in the MS population. However, I would note that the labeling has a paragraph dedicated to **Hyperglycemia**, and specifically mentions a **greater percentage of patients with increased fasting glucose levels in the ZENEPAX group (32%) as compared to placebo (16%)**. The post-marketing experience section includes severe acute hypersensitivity reactions including anaphylaxis characterized by hypotension, bronchospasm, wheezing, laryngeal edema, pulmonary edema, cyanosis, hypoxia, respiratory arrest, cardiac arrhythmia, cardiac arrest, peripheral edema, loss of consciousness, fever, rash, urticaria, diaphoresis, pruritus, and/or injection site reactions, as well as cytokine release syndrome..

Given the finding of increased fasting glucose, it is surprising that routine glucose levels were not measured in the phase 2 and 3 clinical trials. Isolated events of acute hypersensitivity were observed with DAC HYP, although not as severe as those observed with ZENEPAX. The label does not mention chronic immune mediated reactions (as those observed with DAC HYP).

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DAC Nutley was evaluated in patients with MS and other indications at the dose of 1 mg/kg monthly, intravenously, some of them with background therapy (IFN β 1a or cyclosporine). There were five small (9 to 21 patients per study), open label phase 2 studies in MS, as well as exploratory studies in psoriasis (DAC-1001 and 1002), asthma (DAC-1003), uveitis and ulcerative colitis. Of note, approximately 10% of patients included in the study in psoriatic patients presented rashes consistent with psoriasis relapse. Common AE in the DAC Nutley studies included rash, lymphadenopathy, respiratory and urinary infections and transaminase elevation. Isolated SAE of infections (including a VZV CNS infection), anaphylactoid reaction, exfoliative dermatitis were reported. *The applicant concluded that DAC Nutley was “well tolerated.” Of note, serum Glucose levels are listed per patient, per visit in the study report, but analyses of change from baseline and outlier analyses are not included. Calcium and phosphorus levels are not presented in the complete study report. The FDA should ask the applicant to present the analyses of glucose, calcium and phosphorus from these studies.*

DAC Penzberg was studied in healthy volunteers (DAC-1004), ulcerative colitis (DAC-1008) and Multiple sclerosis (DAC-1012) at doses of 1 or 2 mg/kg subcutaneous or intravenously, every 2 weeks for up to 8 weeks, with 12 weeks follow up. Of note, in the ulcerative colitis study, 13 of 103 (13%) of patients on DAC Penzberg had and AE of “colitis, ulcerative” as compared to 3 of 56 (5%) exposed to placebo. Of the 13 cases on DAC, 3 were serious AEs, including one who required a proctocolectomy. Other serious AEs in this study included 2 cases of pneumonia, one of “lung neoplasm” (which eventually resolved without specific treatment) and one of multiple myeloma. There was also a “non-serious” melanoma in the DAC group. *The applicant concluded that DAC Penzberg was “well tolerated.” I conclude that DAC Penzberg clearly increased the risk of ulcerative colitis in patients with underlying ulcerative colitis (among other AEs). Of note, glucose and calcium levels were measured in this study; there are listings of results by patient and visit, but no analyses of change from baseline.*

Of these, the largest, and the one used to choose the dose of DAC HYP in study 201 was DAC-1012, as described below.

Study DAC-1012 in MS with DAC PENZBERG

This was a phase 2, randomized, double blinded, placebo-controlled multicenter study of subcutaneous daclizumab Penzberg in patients with active relapsing forms of MS who were taking IFN β 1a. It was conducted in 51 sites (in US, Canada, Germany, Italy and Spain) from May 2005 to September 2007. The objective was to determine the safety profile of daclizumab, to evaluate PK and PD parameters and immunogenicity. The study consisted of a 24-week treatment period (20 weeks of dosing plus 4 weeks of follow up), followed by a 48-week washout period (during which patients did not receive study drug, but continued on IFN- β therapy for at least 5 months of the 48 weeks).

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The primary endpoint were MRI lesions. Secondary endpoints included the incidence of anti DAC antibodies and adverse events for DAC Penzberg as compared to placebo. Additionally, there was measurement of PK parameters, exploratory PD assessments (T lymphocyte response to general stimulation, lymphocyte phenotyping [T, B, NK and cd25+ cells]), and immunogenicity assessments (anti-DAC antibodies using ELISA). Neutralizing antibodies to IFNβ1a were also measured. Autoantibodies were measured at baseline, Day 504 and as deemed appropriate by the investigator or clinical monitor.

A total of 288 patients were screened and 230 were randomized; 214 (93%) completed 24 weeks of treatment and 194 (84%) completed follow-up through Week 72. Eligibility criteria were standard for MS trials. Treatment groups (given as two subcutaneous doses):

- *High dose*: Daclizumab SC: 2 mg/kg every 2 weeks × 11 doses
(maximum dose: 200 mg per dosing visit)
- *Low Dose*: Daclizumab SC: 1 mg/kg every 4 weeks × 6 doses
(maximum dose: 100 mg per dosing visit), alternating with placebo SC every 4 weeks × 5 doses
- *Placebo*: Placebo SC every 2 weeks × 11 doses

Results (as per the submitted CSR)

Efficacy: On a background of stable IFN-beta therapy, patients treated with DAC Penzberg 2 mg/kg every 2 weeks had 72% fewer new or enlarged Gd-CELS between Weeks 8 and 24 than patients in the placebo group (p=0.0038). Patients in the low dose daclizumab group (1 mg/kg every 4 weeks) had 25% fewer new or enlarged Gd-CELS compared to the placebo group (p=0.5138). **There is evidence of dose response in terms of efficacy.**

Safety: There were no deaths. Serious AEs were reported in 13% vs. 5% of patients on DAC Penzberg and placebo, respectively (mostly infections followed by hepatobiliary disorders). There were a few AE leading to drug discontinuation (5 in total). The overall incidence of AEs was similar between daclizumab-treated and placebo-treated patients but Grade 3 AEs occurred in approximately 24% of daclizumab-treated patients compared with 14% of placebo-treated patients. Grade 4 AEs occurred in 2 placebo-treated patients (coronary artery disease, suicidal ideation) and 2 high dose daclizumab-treated patients (depressed level of consciousness and multiorgan hypersensitivity [patient 8107 described below]). There were no relevant/consistent changes in laboratory, vital signs and ECG evaluations. **There is no clear dose response in terms of safety.** AE analyses are summarized below.

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13.3.19.2 Summary of AEs in study DAC-1012

	Placebo N=77 n (%)	DAC PENZBERG 1 mg/kg N=78 n (%)	DAC PENZBERG 2 mg/kg N=75 n (%)
Any AE	75 (97.4)	78 (100)	71 (94)
Any SAE	4 (5.2)	9 (11.5)	11 (14.7)
Any AE leading to WD	1 (1.3)	3 (3.8)	1 (1.3)

Source: Table 12-2 CSR. AE: adverse events. SAE: serious AE. WD: withdrawal.

Subject 8107. 33 year old F. Enrolled in DAC-1012 and received 11 doses of daclizumab 2 mg/kg SC every 2 weeks. First dose was in (b) (6). She had no allergies. Medical history included Ardystil syndrome (bronchiolitis obliterans with organizing pneumonia). Concomitant meds included estrogen, clorazepic, interferon and ibuprofen. Upon the first dose she developed arm erythema, which resolved the same day. Upon the second dose she presented bilateral arm erythema, which resolved without treatment 10 days later. No further erythema was reported. Last dose of daclizumab 2 mg/kg was on (b) (6). On (b) (6) (2 ½ months after last dose) she was diagnosed with **cutaneous rash**, and five days later with **lymphocytic meningitis**. On (b) (6) (3 months after last dose) she was hospitalized because of persistent headache and rash. CSF was clear with mononuclear cells (46/mm³). She was treated with topical steroids and methylprednisolone. She was discharged on (b) (6). On (b) (6) she was re-hospitalized with lymphocytic meningitis and discharged on (b) (6). On (b) (6) she was hospitalized with a suspected urinary tract infection treated with levofloxacin. She still had a cutaneous rash. On (b) (6) the patient was diagnosed with **toxic hepatitis**. **At that time, she was receiving isoniazide**, rifampicin, pyrazinamide and difluconazole (empirical treatment for tuberculosis). TB treatment was discontinued. On (b) (6) she was diagnosed with **Grade 4 interstitial pneumonia**. On (b) (6) she had **cardiopulmonary arrest, requiring resuscitation**. She was hypotensive, oliguric, thrombocytopenic and anemic. Her cutaneous rash increased in severity and described as desquamative, with appearance of psoriasis on the scalp, heels, back and hands. After 12 days, the patient emerged from a **coma**. The rash continued to worsen. Biopsies were inconclusive. The latest biopsy suggested a psoriasis-like event. She was treated with immunoglobulins, topical steroids and methotrexate. The patient was first transferred to a rehabilitation unit and discharged home (b) (6). On (b) (6) – almost 9 months after the last dose of daclizumab- she was hospitalized with **hypereosinophilia** (9%), fever and cutaneous rash. She was treated with immunoglobulins and ceftriaxone. Fever resolved on (b) (6). On (b) (6) the patient developed tachypnea and hypoxemia. CT showed bilateral interstitial infiltrated and bilateral axillary adenopathy. She was diagnosed with interstitial pneumonitis and treated with cyclosporine, prednisone, methylprednisolone. Patient improved and was discharged (b) (6).

Reviewer Comment: This patient appears to have developed a full multiorgan hypersensitivity/DRESS syndrome with rash, aseptic meningitis, eosinophilia, and pneumonitis.

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The patient had a history of Ardystill syndrome (also known as BOOP [bronchiolitis obliterans with organizing pneumonia]) and may have a predisposition to autoimmune diseases.

Additionally, the patient had hepatitis attributed to isoniazide which she was apparently given for possible tuberculosis for an unknown duration. The narrative is unclear as to whether the patient really had tuberculosis. It is also unclear why a patient with history of immune mediated lung disease would be included in a phase 2 study of a new biologic agent.

This DRESS-like event with multiorgan failure occurred with daclizumab Penzberg, not daclizumab HYP. The applicant sustains that the safety/immunogenicity of one formulation does not apply to the other. However, similar events were observed in the phase 2 and 3 studies of DAC HYP (e.g. patient with Kawasaki syndrome).

A SAE of **adrenal insufficiency** was also reported in the daclizumab low dose group.

AE leading to drug withdrawal included patient 1904 (Hypersensitivity), patient 8204 (fever) and patient 2910 (hepatic enzymes increased), after 6, 8 and 9 doses, respectively.

There were two AE of hyponatremia, one serious, associated with hypokalemia (DAC1012-1202) on daclizumab Penzberg 2mg/day and one “non-serious” (DAC1012-7604, on daclizumab Penz 1 mg/kg; patient had 2 episodes, one of sodium <129 mEq/L and one reported as requiring ER for >24 hours). Both recovered.

Review of AE datasets for this study identified two patients with non-SAE of colitis, both on daclizumab Penz 1 mg/kg. One had recurrent flares of ulcerative colitis (patient DAC1202-2209) and the other had “collagenous colitis” (DAC1202-6301). No action was taken with drug. Both eventually resolved. No narratives were submitted.

Cutaneous events occurred in 45% of daclizumab 1 mg/kg and 32% of daclizumab 2 mg/kg groups (rashes, eczema, psoriasis, urticaria, drug hypersensitivity) and 26% of placebo treated patients. There was greater number of eczema/psoriasis cases on daclizumab as compared to placebo. Of note, there were 5 cases of psoriasis in this study on daclizumab Penz (and none on placebo). Four were on daclizumab Penz 2 mg/kg and one was on the 1mg/kg dose. All were non-SAE, did not lead to drug WD and resolved (one of them, with sequelae).

PK/PD: AS per this study report, Daclizumab treatment caused a 25% reduction from baseline in CD4+ T cells without evidence of dose response. Tcell depletion was not observed. There was increase in NK cells for both doses. There were no changes in Bcell counts. Cell-mediated immunity, as determined using the Cylex@ assay, did not appear to be reduced.

Immunogenicity: A total of 24/152 (15.8%) daclizumab-treated patients were Anti DAC Ab positive, and 12/152 (7.9) had antidaclizumab Neutralizing Ab. Of the NAb positive patients,

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only 4 became NAb positive during the dosing period and drug levels subsequently became not quantifiable, suggesting a loss of drug exposure with NAb response.

Laboratory measurements:

This study included routine hematology and chemistry, including blood glucose. The numbers of patients who had glucose values above or below normal (flagged as hyperglycemia or hypoglycemia, respectively) were similarly distributed among arms. Regarding hyperglycemia, 5 on DAC 1mg, 12 on DAC 2 mg and 10 on placebo had hyperglycemia. Regarding calcium, one patient in the DAC 1mg and one on placebo had at least one measurement of “high calcium”, and four patients had at least one “low calcium” one on each active treatment group and two on placebo. Analyses of changes from baseline are not included.

In summary, in general, evaluation of safety in the DAC Penzberg study 1202 was consistent with that observed in the Phase 2/3 DAC HYP trials. One patient presented multiorgan failure consistent with DRESS similar to the case of Kawasaki syndrome and one had adrenal insufficiency. This trial included glucose and calcium measurements. There were no overt abnormalities of blood glucose or calcium levels, which is reassuring but the dataset is small and lack of signals cannot be extrapolated to the phase 2/3 trials with DAC HYP.

- Postmarketing data from another anti-CD25 agent in the class (BASILIXIMAB, Simulect®)

Basiliximab is a chimeric (murine/human) anti-CD25 antibody marketed by Novartis as Simulect and is indicated for prophylaxis of acute organ rejection in patients receiving renal transplant when used as part of an immunosuppressive regimen that includes cyclosporine and corticosteroids. The label carries a boxed WARNING that only physicians experienced in immunosuppression therapy and management of organ transplantation patients should prescribe basilixumab, and that patients receiving the drug should be managed in facilities with adequate staff, laboratory and supportive medical resources.

Simulect is contraindicated in patients with history of hypersensitivity to basiliximab or any other component of the formulation. “Severe acute (onset within 24 hours) hypersensitivity reactions including anaphylaxis have been observed both on initial exposure to Simulect and/or following re-exposure after several months. These reactions may include hypotension, tachycardia, cardiac failure, dyspnea, wheezing, bronchospasm, pulmonary edema, respiratory failure, urticaria, rash, pruritus, and/or sneezing.” Of note, among the AE reported in >10% of Simulect-treated patients in placebo-controlled trials included hyperkalemia, hypokalemia, hyperglycemia, hypercholesterolemia, hypophosphatemia, hyperuricemia, although it appears that the percentage was similar to those of placebo patients.

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The applicant argues that the DAC HYP is structurally and pharmacologically different from DAC Penzberg and other DAC formulations. The safety profile observed – or not observed – with Zenepax and Simulect may not apply to DAC HYP, because the population, dosing and schedule for those products are different from that of DAC HYP. However, notwithstanding the small size of the studies, the kind of AEs observed with DAC Nutley and Penzberg in non-transplant patients appears similar to those in phase 2 and 3 trials of DAC HYP including eczema, psoriasis, lymphadenopathy, liver enzyme elevation and colitis. There were no deaths but one patient almost died of DRESS/multiorgan failure (similar to the case of Kawasaki syndrome observed with DAC HYP).

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/s/

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03/23/2016

SALLY U YASUDA
03/24/2016