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RESEARCH**

APPLICATION NUMBER:

761029Orig1s000

OTHER REVIEW(S)

PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for *each* PMR/PMC in the Action Package.

NDA/BLA # 761029
Product Name: ZINBRYTA (daclizumab)

PMR/PMC Description: #3084-1: Conduct a prospective observational study of patients enrolled in the Zinbryta (daclizumab) Risk Evaluation and Mitigation Strategies (REMS) registry, with the primary objective of determining the incidence rates of drug induced liver injury, serious infections, and immune-mediated disorders, including hepatitis, non-infectious colitis, serious skin reactions, Type I diabetes, thyroid disease, sarcoidosis, and other immune disorders. All patients enrolled in the registry should be followed for the duration of treatment and at least 6 months following discontinuation of treatment. The protocol should specify at least two appropriate comparator populations to which the observed incidence rates will be compared.

PMR/PMC Schedule Milestones:	Draft Protocol Submission	09/2016
	Final Protocol Submission:	12/2016
	Study/Trial Completion:	12/2029
	Final Report Submission:	12/2030
	Other:	MM/DD/YYYY

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- Unmet need
- Life-threatening condition
- Long-term data needed
- Only feasible to conduct post-approval
- Prior clinical experience indicates safety
- Small subpopulation affected
- Theoretical concern
- Other

The data obtained from this study will provide longer-term safety data in a larger population than would be feasible prior to approval. The risks were identified in clinical trials prior to approval. The post-approval study will allow for characterization of these serious adverse reactions in a setting outside of the controlled trial experience.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the “new safety information.”

There is a known risk of drug-induced liver injury, serious infections, and immune-mediated disorders after administration of ZINBRYTA. The goal is to characterize the risk when the drug is used outside of a clinical trial setting and in comparison to other relevant populations.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.

If not a PMR, skip to 4.

– **Which regulation?**

- Accelerated Approval (subpart H/E)
- Animal Efficacy Rule
- Pediatric Research Equity Act
- FDAAA required safety study/clinical trial

– **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

- Assess a known serious risk related to the use of the drug?
- Assess signals of serious risk related to the use of the drug?
- Identify an unexpected serious risk when available data indicate the potential for a serious risk?

– **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

Analysis of spontaneous postmarketing adverse events?

Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk

Analysis using pharmacovigilance system?

Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk

Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?

Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk

Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

Conduct a prospective observational study of patients enrolled in the Zinbryta (daclizumab) Risk Evaluation and Mitigation Strategies (REMS) registry, with the primary objective of determining the incidence rates of drug induced liver injury, serious infections, and immune-mediated disorders, including hepatitis, non-infectious colitis, serious skin reactions, Type I diabetes, thyroid disease, sarcoidosis, and other immune disorders. All patients enrolled in the registry should be followed for the duration of treatment and at least 6 months following discontinuation of treatment. The protocol should specify at least two appropriate comparator populations to which the observed incidence rates will be compared.

Required

- Observational pharmacoepidemiologic study
- Registry studies
- Primary safety study or clinical trial
- Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- Thorough Q-T clinical trial
- Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
- Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
- Pharmacokinetic studies or clinical trials
- Drug interaction or bioavailability studies or clinical trials
- Dosing trials

Continuation of Question 4

- Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)

- Meta-analysis or pooled analysis of previous studies/clinical trials
- Immunogenicity as a marker of safety
- Other (provide explanation)

Agreed upon:

- Quality study without a safety endpoint (e.g., manufacturing, stability)
- Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
- Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
- Dose-response study or clinical trial performed for effectiveness
- Nonclinical study, not safety-related (specify)

- Other

5. Is the PMR/PMC clear, feasible, and appropriate?

- Does the study/clinical trial meet criteria for PMRs or PMCs?
- Are the objectives clear from the description of the PMR/PMC?
- Has the applicant adequately justified the choice of schedule milestone dates?
- Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

Check if this form describes a FDAAA PMR that is a randomized controlled clinical trial

If so, does the clinical trial meet the following criteria?

- There is a significant question about the public health risks of an approved drug
- There is not enough existing information to assess these risks
- Information cannot be gained through a different kind of investigation
- The trial will be appropriately designed to answer question about a drug's efficacy and safety, and
- The trial will emphasize risk minimization for participants as the protocol is developed

PMR/PMC Development Coordinator:

This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.

(signature line for BLAs)

PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for ***each*** PMR/PMC in the Action Package.

NDA/BLA # 761029
Product Name: ZINBRYTA (daclizumab)

PMR/PMC Description: #3084-2: Conduct a prospective observational study of patients enrolled in the Zinbryta (daclizumab) REMS registry, with the primary objective of determining the incidence and mortality rates of breast cancer. All patients enrolled in the registry should be followed for a minimum of 10 years or until death following their first exposure to Zinbryta (daclizumab). The protocol should specify at least two appropriate comparator populations to which the observed incidence and mortality rates will be compared.

PMR/PMC Schedule Milestones:	Draft Protocol Submission	10/2016
	Final Protocol Submission	01/2017
	Study/Trial Completion:	06/2030
	Final Report Submission:	06/2031
	Other: Interim Report Submission	06/2019
		06/2021
		06/2023
		06/2025
		06/2027
		06/2029

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- Unmet need
- Life-threatening condition
- Long-term data needed
- Only feasible to conduct post-approval
- Prior clinical experience indicates safety
- Small subpopulation affected
- Theoretical concern
- Other

The data obtained from this study will provide longer-term safety data in a larger population than would be feasible prior to approval. A signal for the risk of breast cancer was identified in clinical trials prior to approval. The post-approval study will allow for characterization of this serious adverse reaction.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the “new safety information.”

There is a signal for a risk of breast cancer in men and in women after administration of Zinbryta that was primarily detected in the uncontrolled extension studies that did not have comparator groups. The goal of this study is to characterize the risk and consider the risk with respect to appropriate comparator populations..

3. If the study/clinical trial is a **PMR**, check the applicable regulation.

If not a PMR, skip to 4.

– **Which regulation?**

- Accelerated Approval (subpart H/E)
 Animal Efficacy Rule
 Pediatric Research Equity Act
 FDAAA required safety study/clinical trial

– **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

- Assess a known serious risk related to the use of the drug?
 Assess signals of serious risk related to the use of the drug?
 Identify an unexpected serious risk when available data indicate the potential for a serious risk?

– **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

- Analysis of spontaneous postmarketing adverse events?

Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk

- Analysis using pharmacovigilance system?

Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk

- Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?

Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk

- Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

Conduct a prospective observational study of patients enrolled in the Zinbryta (daclizumab) REMS registry, with the primary objective of determining the incidence and mortality rates of breast cancer. All patients enrolled in the registry should be followed for a minimum of 10 years or until death following their first exposure to Zinbryta (daclizumab). The protocol should specify at least two appropriate comparator populations to which the observed incidence and mortality rates will be compared.

Required

- Observational pharmacoepidemiologic study
- Registry studies
- Primary safety study or clinical trial
- Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- Thorough Q-T clinical trial
- Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
- Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
- Pharmacokinetic studies or clinical trials
- Drug interaction or bioavailability studies or clinical trials
- Dosing trials

Continuation of Question 4

- Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)

- Meta-analysis or pooled analysis of previous studies/clinical trials
- Immunogenicity as a marker of safety
- Other (provide explanation)

Agreed upon:

- Quality study without a safety endpoint (e.g., manufacturing, stability)
- Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
- Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
- Dose-response study or clinical trial performed for effectiveness
- Nonclinical study, not safety-related (specify)

- Other

5. Is the PMR/PMC clear, feasible, and appropriate?

- Does the study/clinical trial meet criteria for PMRs or PMCs?
- Are the objectives clear from the description of the PMR/PMC?
- Has the applicant adequately justified the choice of schedule milestone dates?
- Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

Check if this form describes a FDAAA PMR that is a randomized controlled clinical trial

If so, does the clinical trial meet the following criteria?

- There is a significant question about the public health risks of an approved drug
- There is not enough existing information to assess these risks
- Information cannot be gained through a different kind of investigation
- The trial will be appropriately designed to answer question about a drug's efficacy and safety, and
- The trial will emphasize risk minimization for participants as the protocol is developed

PMR/PMC Development Coordinator:

- This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

(signature line for BLAs)

PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for *each* PMR/PMC in the Action Package.

NDA/BLA # 761029
Product Name: ZINBRYTA (daclizumab)

PMR/PMC Description: #3084-3: Conduct a nested case-control study among patients enrolled in the Zinbryta (daclizumab) REMS registry, with the primary objective of determining which clinical attributes are risk factors or protective factors for developing liver disorders and serious skin reactions. Determine whether there are biomarkers that are earlier indicators of liver injury than standard liver function tests. Patient blood samples will need to be analyzed at baseline, 3 months, and 6 months after initiating therapy and possibly when ending therapy. At a minimum, the following potential risk factors must be evaluated:

- a. Demographic characteristics (age, gender, race).
- b. Cumulative dose exposure to daclizumab.
- c. Prior history of immune disorders, including autoimmune hepatitis.
- d. Genomic risk factors.
- e. T-cell markers, such as FOX-3, CD-25 and others.
- f. Other concomitant drug use.
- g. Comorbidities.
- h. Prior drug use to treat MS.
- i. Prior adverse events as a result of MS drug treatment, including drug-induced liver injury.
- j. Exposure to high-dose intravenous methylprednisolone, steroids, and other immune suppressants.
- k. Time between exposures (daclizumab, other MS drugs, and immune suppressants) and development of serious adverse events.

PMR/PMC Schedule Milestones:	Draft Protocol Submission	10/2016
	Final Protocol Submission:	12/2016
	Study/Trial Completion:	12/2027
	Final Report Submission:	12/2028
	Other:	MM/DD/YYYY

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- Unmet need
- Life-threatening condition
- Long-term data needed
- Only feasible to conduct post-approval
- Prior clinical experience indicates safety
- Small subpopulation affected
- Theoretical concern
- Other

The data obtained from this study may require long-term exposure in a larger population than available at the time of approval in order to characterize risk factors (or protective factors) for serious adverse reactions for which the signals may be relatively small. The serious adverse reactions are of liver toxicity and serious skin reactions are known and can be described in labeling.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the “new safety information.”

The use of Zinbryta is associated with serious liver toxicity and serious skin reactions. The goal of the study is to identify risk factors or protective factors for developing these serious adverse reactions.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.
If not a PMR, skip to 4.

– **Which regulation?**

- Accelerated Approval (subpart H/E)
- Animal Efficacy Rule
- Pediatric Research Equity Act
- FDAAA required safety study/clinical trial

– **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

- Assess a known serious risk related to the use of the drug?
- Assess signals of serious risk related to the use of the drug?
- Identify an unexpected serious risk when available data indicate the potential for a serious risk?

– **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

- Analysis of spontaneous postmarketing adverse events?

Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk

Analysis using pharmacovigilance system?

Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk

Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?

Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk

Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

Conduct a nested case-control study among patients enrolled in the Zinbryta (daclizumab) REMS registry, with the primary objective of determining which clinical attributes are risk factors or protective factors for developing liver disorders and serious skin reactions. Determine whether there are biomarkers that are earlier indicators of liver injury than standard liver function tests. Patient blood samples will need to be analyzed at baseline, 3 months, and 6 months after initiating therapy and possibly when ending therapy. At a minimum, the following potential risk factors must be evaluated:

- a. Demographic characteristics (age, gender, race).
- b. Cumulative dose exposure to daclizumab.
- c. Prior history of immune disorders, including autoimmune hepatitis.
- d. Genomic risk factors.
- e. T-cell markers, such as FOXP-3, CD-25 and others.
- f. Other concomitant drug use.
- g. Comorbidities.
- h. Prior drug use to treat MS.
- i. Prior adverse events as a result of MS drug treatment, including drug-induced liver injury.
- j. Exposure to high-dose intravenous methylprednisolone, steroids, and other immune suppressants.
- k. Time between exposures (daclizumab, other MS drugs, and immune suppressants) and development of serious adverse events.

Required

- Observational pharmacoepidemiologic study
- Registry studies
- Primary safety study or clinical trial
- Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- Thorough Q-T clinical trial
- Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
- Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
- Pharmacokinetic studies or clinical trials
- Drug interaction or bioavailability studies or clinical trials
- Dosing trials

Continuation of Question 4

- Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)

-
- Meta-analysis or pooled analysis of previous studies/clinical trials
 - Immunogenicity as a marker of safety
 - Other (provide explanation)
-

Agreed upon:

- Quality study without a safety endpoint (e.g., manufacturing, stability)
- Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
- Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
- Dose-response study or clinical trial performed for effectiveness
- Nonclinical study, not safety-related (specify)

-
- Other
-

5. Is the PMR/PMC clear, feasible, and appropriate?

- Does the study/clinical trial meet criteria for PMRs or PMCs?
- Are the objectives clear from the description of the PMR/PMC?
- Has the applicant adequately justified the choice of schedule milestone dates?
- Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

- Check if this form describes a FDAAA PMR that is a randomized controlled clinical trial

If so, does the clinical trial meet the following criteria?

- There is a significant question about the public health risks of an approved drug
- There is not enough existing information to assess these risks
- Information cannot be gained through a different kind of investigation
- The trial will be appropriately designed to answer question about a drug's efficacy and safety, and
- The trial will emphasize risk minimization for participants as the protocol is developed

PMR/PMC Development Coordinator:

This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.

(signature line for BLAs)

PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for *each* PMR/PMC in the Action Package.

NDA/BLA # 761029
Product Name: ZINBRYTA (daclizumab)

PMR/PMC Description: #3084-4: Conduct prospective pregnancy exposure registry cohort analyses in the United States that compare the maternal, fetal, and infant outcomes of women with multiple sclerosis exposed to Zinbryta (daclizumab) during pregnancy with two unexposed control populations: one comprised of women with multiple sclerosis who have not been exposed to Zinbryta (daclizumab) before or during pregnancy and the other comprised of women without multiple sclerosis. The registry will identify and record pregnancy complications, major and minor congenital malformations, spontaneous abortions, stillbirths, elective terminations, preterm births, small-for-gestational-age births, and any other adverse outcomes, including postnatal growth and development. Outcomes will be assessed through at least the first year of life.

PMR/PMC Schedule Milestones:	Draft Protocol Submission	06/2016
	Final Protocol Submission:	08/2016
	Study/Trial Completion:	08/2027
	Final Report Submission:	08/2028
	Interim Report Submission:	08/2018
		08/2020
		08/2022
		08/2024
		08/2026

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- Unmet need
- Life-threatening condition
- Long-term data needed
- Only feasible to conduct post-approval
- Prior clinical experience indicates safety
- Small subpopulation affected
- Theoretical concern
- Other

Pregnancy registries are conducted post-marketing to obtain safety data on drug use during pregnancy including maternal and infant outcomes. Historically, pregnancy registries are not conducted during the pre-marketing period, because except in unusual circumstances, it is ethically and medically important to demonstrate safety and efficacy in nonpregnant women before studying the drug in pregnant women.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the “new safety information.”

There are no adequate data on the developmental risk associated with use of Zinbryta in pregnant women. Administration of Zinbryta to monkeys during gestation resulted in embryofetal death at maternal exposures higher than that expected clinically. The goal of the pregnancy registry is to obtain data on Zinbryta exposure during pregnancy including data on infant outcomes to inform prescribing for and counseling of women affected by multiple sclerosis that are pregnant and of childbearing potential.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.
If not a PMR, skip to 4.

– **Which regulation?**

- Accelerated Approval (subpart H/E)
 Animal Efficacy Rule
 Pediatric Research Equity Act
 FDAAA required safety study/clinical trial

– **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

- Assess a known serious risk related to the use of the drug?
 Assess signals of serious risk related to the use of the drug?
 Identify an unexpected serious risk when available data indicate the potential for a serious risk?

– **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

- Analysis of spontaneous postmarketing adverse events?
Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk
- Analysis using pharmacovigilance system?
Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk
- Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk
- Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

Conduct prospective pregnancy exposure registry cohort analyses in the United States that compare the maternal, fetal, and infant outcomes of women with multiple sclerosis exposed to Zinbryta (daclizumab) during pregnancy with two unexposed control populations: one with women with multiple sclerosis who have not been exposed to Zinbryta (daclizumab) before or during pregnancy and the other in women without multiple sclerosis. The registry will identify and record pregnancy complications, major and minor congenital malformations, spontaneous abortions, stillbirths, elective terminations, preterm births, small-for-gestational-age births, and any other adverse outcomes, including postnatal growth and development, and will be assessed through at least the first year of life.

Required

- Observational pharmacoepidemiologic study
 Registry studies
 Primary safety study or clinical trial
 Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
 Thorough Q-T clinical trial
 Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
 Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
 Pharmacokinetic studies or clinical trials
 Drug interaction or bioavailability studies or clinical trials
 Dosing trials

Continuation of Question 4

- Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)
-
- Meta-analysis or pooled analysis of previous studies/clinical trials
 Immunogenicity as a marker of safety
 Other (provide explanation)
-

Agreed upon:

- Quality study without a safety endpoint (e.g., manufacturing, stability)
 Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
 Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
 Dose-response study or clinical trial performed for effectiveness
 Nonclinical study, not safety-related (specify)
-
- Other
-

5. Is the PMR/PMC clear, feasible, and appropriate?

- Does the study/clinical trial meet criteria for PMRs or PMCs?
- Are the objectives clear from the description of the PMR/PMC?
- Has the applicant adequately justified the choice of schedule milestone dates?
- Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

Check if this form describes a FDAAA PMR that is a randomized controlled clinical trial

If so, does the clinical trial meet the following criteria?

- There is a significant question about the public health risks of an approved drug
- There is not enough existing information to assess these risks
- Information cannot be gained through a different kind of investigation
- The trial will be appropriately designed to answer question about a drug's efficacy and safety, and
- The trial will emphasize risk minimization for participants as the protocol is developed

PMR/PMC Development Coordinator:

- This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

(signature line for BLAs)

PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for *each* PMR/PMC in the Action Package.

NDA/BLA # 761029
Product Name: ZINBRYTA (daclizumab)

PMR/PMC Description: #3084-5: Develop and validate an assay with improved sensitivity for the detection of neutralizing antibodies against daclizumab in the presence of daclizumab levels that are expected in samples collected from patients on treatment.

PMR/PMC Schedule Milestones: Final Protocol Submission: 01/2017
Final Report Submission: 01/2019
Other: MM/DD/YYYY

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- Unmet need
- Life-threatening condition
- Long-term data needed
- Only feasible to conduct post-approval
- Prior clinical experience indicates safety
- Small subpopulation affected
- Theoretical concern
- Other

The safety profile observed in clinical studies indicates that the presence of anti-drug antibodies does not appear to be a significant safety issue. The presence of neutralizing anti-drug antibodies may affect PK. The development and implementation of a more sensitive assay for detecting neutralizing anti-drug-antibodies (ADAs) would provide better assessment and characterization of the patients' ADA response to daclizumab.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the "new safety information."

The current methods for detecting neutralizing anti-drug antibody (ADA) are not tolerant to the presence of drug at the levels expected to be in some patients' serum at the time of sampling, leading to a reduced capability of detecting ADA.

The goal of the study is to develop and validate an assay with improved sensitivity for the detection of neutralizing antibodies against daclizumab in the presence of daclizumab levels that are expected to be present in samples at the time of patient sampling.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.

If not a PMR, skip to 4.

– **Which regulation?**

- Accelerated Approval (subpart H/E)
- Animal Efficacy Rule
- Pediatric Research Equity Act
- FDAAA required safety study/clinical trial

– **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

- Assess a known serious risk related to the use of the drug?
- Assess signals of serious risk related to the use of the drug?
- Identify an unexpected serious risk when available data indicate the potential for a serious risk?

– **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

- Analysis of spontaneous postmarketing adverse events?

Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk

- Analysis using pharmacovigilance system?

Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk

- Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?

Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk

- Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

Develop and validate an assay with improved sensitivity for the detection of neutralizing antibodies against daclizumab in the presence of daclizumab levels that are expected in samples collected from patients on treatment.

Required

- Observational pharmacoepidemiologic study
- Registry studies
- Primary safety study or clinical trial
- Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- Thorough Q-T clinical trial
- Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
- Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
- Pharmacokinetic studies or clinical trials
- Drug interaction or bioavailability studies or clinical trials
- Dosing trials

Continuation of Question 4

- Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)

-
- Meta-analysis or pooled analysis of previous studies/clinical trials
 - Immunogenicity as a marker of safety
 - Other (provide explanation)
-

Agreed upon:

- Quality study without a safety endpoint (e.g., manufacturing, stability)
- Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
- Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
- Dose-response study or clinical trial performed for effectiveness
- Nonclinical study, not safety-related (specify)

-
- Other
-

5. Is the PMR/PMC clear, feasible, and appropriate?

- Does the study/clinical trial meet criteria for PMRs or PMCs?
- Are the objectives clear from the description of the PMR/PMC?
- Has the applicant adequately justified the choice of schedule milestone dates?
- Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

- Check if this form describes a FDAAA PMR that is a randomized controlled clinical trial

If so, does the clinical trial meet the following criteria?

- There is a significant question about the public health risks of an approved drug
- There is not enough existing information to assess these risks
- Information cannot be gained through a different kind of investigation
- The trial will be appropriately designed to answer question about a drug's efficacy and safety, and
- The trial will emphasize risk minimization for participants as the protocol is developed

PMR/PMC Development Coordinator:

This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.

(signature line for BLAs)

PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for *each* PMR/PMC in the Action Package.

NDA/BLA # 761029
Product Name: ZINBRYTA (daclizumab)

PMR/PMC Description: PMC # 3084-6 : Re-evaluate the (b) (4) charge variant specification for drug substance after 30 lots have been manufactured using the commercial manufacturing process or 3 years post-approval, whichever is sooner. Provide a final report that includes data, the statistical analysis, and proposed changes to the specifications.

PMR/PMC Schedule Milestones: Final Protocol Submission: MM/DD/YYYY
Study/Trial Completion: MM/DD/YYYY
Final Report Submission: 05/2019
Other: MM/DD/YYYY

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- Unmet need
- Life-threatening condition
- Long-term data needed
- Only feasible to conduct post-approval
- Prior clinical experience indicates safety
- Small subpopulation affected
- Theoretical concern
- Other

Data from characterization studies indicate that (b) (4) charge variants in daclizumab do not present a significant risk to potency, immunogenicity, and safety.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the “new safety information.”

The current specification limit for (b) (4) variants in daclizumab drug substance is based on manufacturing capability which reflect a limited number of lots of material. Re-evaluating the specification of (b) (4) charge variants based on data from 30 daclizumab drug substance batches manufactured using the commercial manufacturing process would provide better evaluation of the level of (b) (4) charge variants in daclizumab.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.

If not a PMR, skip to 4.

- **Which regulation?**

- Accelerated Approval (subpart H/E)
- Animal Efficacy Rule
- Pediatric Research Equity Act
- FDAAA required safety study/clinical trial

- **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

- Assess a known serious risk related to the use of the drug?
- Assess signals of serious risk related to the use of the drug?
- Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

- Analysis of spontaneous postmarketing adverse events?
Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk
- Analysis using pharmacovigilance system?
Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk
- Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk
- Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

Re-evaluate the (b) (4) charge variant specification for drug substance after 30 lots have been manufactured using the commercial manufacturing process or 3 years post-approval, whichever is sooner. Provide a final report that includes data, the statistical analysis, and proposed changes to the specifications.

Required

- Observational pharmacoepidemiologic study
- Registry studies
- Primary safety study or clinical trial
- Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- Thorough Q-T clinical trial
- Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
- Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
- Pharmacokinetic studies or clinical trials
- Drug interaction or bioavailability studies or clinical trials
- Dosing trials

Continuation of Question 4

Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)

Meta-analysis or pooled analysis of previous studies/clinical trials

Immunogenicity as a marker of safety

Other (provide explanation)

Agreed upon:

Quality study without a safety endpoint (e.g., manufacturing, stability)

Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)

Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E

Dose-response study or clinical trial performed for effectiveness

Nonclinical study, not safety-related (specify)

Other

5. Is the PMR/PMC clear, feasible, and appropriate?

Does the study/clinical trial meet criteria for PMRs or PMCs?

Are the objectives clear from the description of the PMR/PMC?

Has the applicant adequately justified the choice of schedule milestone dates?

Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

Check if this form describes a FDAAA PMR that is a randomized controlled clinical trial

If so, does the clinical trial meet the following criteria?

There is a significant question about the public health risks of an approved drug

There is not enough existing information to assess these risks

Information cannot be gained through a different kind of investigation

The trial will be appropriately designed to answer question about a drug's efficacy and safety, and

The trial will emphasize risk minimization for participants as the protocol is developed

PMR/PMC Development Coordinator:

This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.

(signature line for BLAs)

PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for *each* PMR/PMC in the Action Package.

NDA/BLA # 761029
Product Name: ZINBRYTA (daclizumab)

PMR/PMC Description: #3084-7: Re-evaluate the (b) (4) charge variant specification for the drug product after manufacturing 30 lots using the commercial manufacturing process or 3 years post-approval, whichever is sooner. Provide a final report that includes data, the statistical analysis, and proposed changes to the specifications.

PMR/PMC Schedule Milestones:	Final Protocol Submission:	<u>MM/DD/YYYY</u>
	Study/Trial Completion:	<u>MM/DD/YYYY</u>
	Final Report Submission:	<u>05/2019</u>
	Other:	<u>MM/DD/YYYY</u>

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- Unmet need
- Life-threatening condition
- Long-term data needed
- Only feasible to conduct post-approval
- Prior clinical experience indicates safety
- Small subpopulation affected
- Theoretical concern
- Other

Data from characterization studies indicate that (b) (4) charge variants in daclizumab do not present a significant risk to potency, immunogenicity, and safety.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the “new safety information.”

The current specification limit for (b) (4) variants in daclizumab DP is based on manufacturing capability which reflects a limited number of lots of material. Re-evaluating the specification of (b) (4) charge variants based on data from 30 daclizumab DP batches manufactured using the commercial manufacturing process would provide better evaluation of the level of (b) (4) charge variants in daclizumab.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.

If not a PMR, skip to 4.

- **Which regulation?**

- Accelerated Approval (subpart H/E)
- Animal Efficacy Rule
- Pediatric Research Equity Act
- FDAAA required safety study/clinical trial

- **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

- Assess a known serious risk related to the use of the drug?
- Assess signals of serious risk related to the use of the drug?
- Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

- Analysis of spontaneous postmarketing adverse events?
Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk
- Analysis using pharmacovigilance system?
Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk
- Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk
- Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

Re-evaluate the ^{(b) (4)} charge variant specification for the drug product after manufacturing 30 lots using the commercial manufacturing process or 3 years post-approval, whichever is sooner. Provide a final report that includes data, the statistical analysis, and proposed changes to the specifications.

Required

- Observational pharmacoepidemiologic study
- Registry studies
- Primary safety study or clinical trial
- Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- Thorough Q-T clinical trial
- Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
- Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
- Pharmacokinetic studies or clinical trials
- Drug interaction or bioavailability studies or clinical trials

Dosing trials
Continuation of Question 4

Additional data or analysis required for a previously submitted or expected study/clinical trial
(provide explanation)

-
- Meta-analysis or pooled analysis of previous studies/clinical trials
 Immunogenicity as a marker of safety
 Other (provide explanation)
-

Agreed upon:

- Quality study without a safety endpoint (e.g., manufacturing, stability)
 Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
 Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
 Dose-response study or clinical trial performed for effectiveness
 Nonclinical study, not safety-related (specify)

Other

5. Is the PMR/PMC clear, feasible, and appropriate?

- Does the study/clinical trial meet criteria for PMRs or PMCs?
 Are the objectives clear from the description of the PMR/PMC?
 Has the applicant adequately justified the choice of schedule milestone dates?
 Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

Check if this form describes a FDAAA PMR that is a randomized controlled clinical trial

If so, does the clinical trial meet the following criteria?

- There is a significant question about the public health risks of an approved drug
 There is not enough existing information to assess these risks
 Information cannot be gained through a different kind of investigation
 The trial will be appropriately designed to answer question about a drug's efficacy and safety, and
 The trial will emphasize risk minimization for participants as the protocol is developed

PMR/PMC Development Coordinator:

- This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

(signature line for BLAs)

PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for *each* PMR/PMC in the Action Package.

NDA/BLA # 761029
Product Name: ZINBRYTA (daclizumab)

PMR/PMC Description: #3084-8: Validate a non-reduced CE-SDS method and evaluate the need for its inclusion in the drug substance and drug product specification. Provide a final report that includes the analytical procedure, validation report, any proposed specification acceptance criteria, and the data used to establish the proposed criteria.

PMR/PMC Schedule Milestones:	Final Protocol Submission:	<u>MM/DD/YYYY</u>
	Study/Trial Completion:	<u>MM/DD/YYYY</u>
	Final Report Submission:	<u>05/2020</u>
	Other:	<u>MM/DD/YYYY</u>

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- Unmet need
- Life-threatening condition
- Long-term data needed
- Only feasible to conduct post-approval
- Prior clinical experience indicates safety
- Small subpopulation affected
- Theoretical concern
- Other

A non-reducing CE-SDS method was used as a characterization assay for daclizumab (b) (4)

This is a common occurrence in recombinant IgG1 antibodies and is not considered to pose a safety risk.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the “new safety information.”

A non-reducing CE-SDS is only used as a characterization assay for daclizumab and is not performed as a release assay for daclizumab DS and DP. The level (b) (4) detected by non-reducing CE-SDS is not monitored currently during daclizumab DS and DP release.

Implementation of non-reducing CE-SDS method into the DS and DP specification would provide better assessment of product purity and trending during routine production with respect to the levels of intact and fragmented daclizumab.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.

If not a PMR, skip to 4.

– **Which regulation?**

- Accelerated Approval (subpart H/E)
- Animal Efficacy Rule
- Pediatric Research Equity Act
- FDAAA required safety study/clinical trial

– **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

- Assess a known serious risk related to the use of the drug?
- Assess signals of serious risk related to the use of the drug?
- Identify an unexpected serious risk when available data indicate the potential for a serious risk?

– **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

- Analysis of spontaneous postmarketing adverse events?

Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk

- Analysis using pharmacovigilance system?

Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk

- Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?

Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk

- Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

Validate a non-reduced CE-SDS method and evaluate the need for its inclusion in the drug substance and drug product specification. Provide a final report that includes the analytical procedure, validation report, any proposed specification acceptance criteria, and the data used to establish the proposed criteria.

Required

- Observational pharmacoepidemiologic study
- Registry studies
- Primary safety study or clinical trial
- Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- Thorough Q-T clinical trial
- Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
- Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
- Pharmacokinetic studies or clinical trials
- Drug interaction or bioavailability studies or clinical trials
- Dosing trials

Continuation of Question 4

- Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)

-
- Meta-analysis or pooled analysis of previous studies/clinical trials
 - Immunogenicity as a marker of safety
 - Other (provide explanation)
-

Agreed upon:

- Quality study without a safety endpoint (e.g., manufacturing, stability)
- Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
- Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
- Dose-response study or clinical trial performed for effectiveness
- Nonclinical study, not safety-related (specify)

-
- Other
-

5. Is the PMR/PMC clear, feasible, and appropriate?

- Does the study/clinical trial meet criteria for PMRs or PMCs?
- Are the objectives clear from the description of the PMR/PMC?
- Has the applicant adequately justified the choice of schedule milestone dates?
- Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

- Check if this form describes a FDAAA PMR that is a randomized controlled clinical trial

If so, does the clinical trial meet the following criteria?

- There is a significant question about the public health risks of an approved drug
- There is not enough existing information to assess these risks
- Information cannot be gained through a different kind of investigation
- The trial will be appropriately designed to answer question about a drug's efficacy and safety, and
- The trial will emphasize risk minimization for participants as the protocol is developed

PMR/PMC Development Coordinator:

This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.

(signature line for BLAs)

PMR/PMC Development Template: Product Quality (CMC)

This template should be completed by the review chemist (ONDQA) or biologist (OBP) and included for *each* type of CMC PMR/PMC in the Action Package. See #4 for a list of CMC PMR/PMC types

NDA/BLA #	761029
Product Name:	ZINBRYTA (daclizumab)
PMC#3084-9	Conduct microbial spiking studies of the (b) (4)
Description:	(b) (4) product intermediates in a small-scale-study to demonstrate that the product intermediates do not support significant microbial growth under the proposed hold conditions.
PMC Schedule Milestones:	Final Protocol Submission: _____
	Study/Trial Completion: _____
	Final Report Submission: 11/2017
	Other: _____

1. During application review, explain why this issue is appropriate for a PMC instead of a pre-approval requirement. Check reason below and describe.

- Need for drug (unmet need/life-threatening condition)
- Long-term data needed (e.g., stability data)
- Only feasible to conduct post-approval
- Improvements to methods
- Theoretical concern
- Manufacturing process analysis
- Other

The sponsor needs to provide additional data to support the hold times to ensure (b) (4) (b) (4) the microbial quality of the product. This is appropriate for a PMC (b) (4) (b) (4) However, supplemental data are needed (b) (4) (b) (4) The study will be conducted under a QA-approved protocol. The acceptance criteria of the protocol were provided in the BLA and were adequate.

2. Describe the particular review issue and the goal of the study.

The hold times of these steps have not been validated at scale. Data from small-scale microbial spiking studies are needed to demonstrate that these product intermediates do not support significant microbial growth under the proposed hold conditions.

3. [OMIT – for PMRs only]

4. What type of study is agreed upon (describe and check type below)?

Select only one. Fill out a new sheet for each type of PMR/PMC study.

- Dissolution testing
- Assay
- Sterility
- Potency
- Product delivery
- Drug substance characterization
- Intermediates characterization
- Impurity characterization
- Reformulation
- Manufacturing process issues
- Other

Describe the agreed-upon study:

Conduct microbial spiking studies of the [REDACTED] (b) (4) [REDACTED] product intermediates in a small-scale-study to demonstrate that the product intermediates do not support significant microbial growth under the proposed hold conditions.

5. To be completed by ONDQA/OBP Manager:

- Does the study meet criteria for PMCs?
- Are the objectives clear from the description of the PMC?
- Has the applicant adequately justified the choice of schedule milestone dates?
- Has the applicant had sufficient time to review the PMCs, ask questions, determine feasibility, and contribute to the development process?

PMR/PMC Development Coordinator:

- This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

(signature line for BLAs only)

PMR/PMC Development Template: Product Quality (CMC)

This template should be completed by the review chemist (ONDQA) or biologist (OBP) and included for *each* type of CMC PMR/PMC in the Action Package. See #4 for a list of CMC PMR/PMC types

NDA/BLA # 761029
Product Name: ZINBRYTA (daclizumab)

PMC#3084-10
Description: Provide endotoxin recovery data from two additional drug product lots spiked with Control Standard Endotoxin (CSE).

PMC Schedule Milestones:

Final Protocol Submission:	_____
Study/Trial Completion:	_____
Final Report Submission:	<u>08/2016</u>
Other:	_____

1. During application review, explain why this issue is appropriate for a PMC instead of a pre-approval requirement. Check reason below and describe.

- Need for drug (unmet need/life-threatening condition)
- Long-term data needed (e.g., stability data)
- Only feasible to conduct post-approval
- Improvements to methods
- Theoretical concern
- Manufacturing process analysis
- Other

Endotoxin spiking and hold study data from one drug product lot were provided and demonstrated adequate recovery of the spiked Control Standard Endotoxin (CSE) (b) (4). Data from two additional drug product lots are needed to confirm the validity of the endotoxin release tests for drug substance and drug product.

This is appropriate for a PMC because the risk assessment for endotoxin control provided by the sponsor concluded minimum risk of endotoxin contamination (b) (4) of the drug substance manufacturing process and in the drug product manufacturing process. The endotoxin test (b) (4) has adequate endotoxin recovery. In addition, the endotoxin specifications for drug substance and drug product are (b) (4) lower than the safety threshold. The risk of endotoxin contamination above the safety threshold level is low.

2. Describe the particular review issue and the goal of the study.

Data from previous endotoxin spiking and hold study demonstrated unacceptable endotoxin recovery (b) (4) using three lots of drug substance (b) (4). Recent endotoxin spiking and hold studies demonstrated acceptable endotoxin recovery (b) (4) using one lot of drug product. Data from two additional drug product lots are needed to confirm the validity of the endotoxin release tests for drug substance and drug product. In addition, the recent endotoxin spiking and hold study using one DP lot showed endotoxin recoveries (b) (4).

The Agency recommended (u) (4)

3. [OMIT – for PMRs only]

4. What type of study is agreed upon (describe and check type below)?

Select only one. Fill out a new sheet for each type of PMR/PMC study.

- Dissolution testing
- Assay
- Sterility
- Potency
- Product delivery
- Drug substance characterization
- Intermediates characterization
- Impurity characterization
- Reformulation
- Manufacturing process issues
- Other

Describe the agreed-upon study:

Provide endotoxin recovery data from two additional drug product lots spiked with Control Standard Endotoxin (CSE).

5. To be completed by ONDQA/OBP Manager:

- Does the study meet criteria for PMCs?
- Are the objectives clear from the description of the PMC?
- Has the applicant adequately justified the choice of schedule milestone dates?
- Has the applicant had sufficient time to review the PMCs, ask questions, determine feasibility, and contribute to the development process?

PMR/PMC Development Coordinator:

- This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

(signature line for BLAs only)

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

/s/

SALLY U YASUDA
05/27/2016

MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING

Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Date of This Memorandum: May 20, 2016

Requesting Office or Division: Division of Neurology Products (DNP)

Application Type and Number: BLA 761029

Product Name and Strength: Zinbryta (daclizumab)* injection
150 mg/mL

* For purposes of this review, we refer to the proposed product as "daclizumab." The Applicant proposed (b) (4) which FDA objected to in (b) (4) the International Nonproprietary Names for Pharmaceutical Substances.

Submission Date: May 19, 2016

Applicant/Sponsor Name: Biogen Inc.

OSE RCM #: 2015-530-1

DMEPA Primary Reviewer: Justine Harris, BS, RPh

DMEPA Team Leader: Danielle Harris, PharmD, BCPS

1 PURPOSE OF MEMO

The Division of Neurology Products (DNP) requested that we review the revised Prescribing Information (PI), Medication Guide (MG), Instructions for Use (IFU), container labels and carton labeling for Zinbryta (Appendix A) to determine if it is acceptable from a medication error perspective. The revisions are in response to recommendations that DMEPA made during a previous label and labeling review¹ and recommendations made by the Office of Biotechnology Products (OBP) reviewer². We note the Applicant withdrew their (b) (4) configuration on ~~March 18, 2016, therefore,~~ (b) (4) labels were not evaluated in this review.

¹ Harris J. Human Factors Label and Labeling Review for ZINBRYTA (BLA 761029) Silver Spring (MD): Food and Drug Administration, Center for Drug Evaluation and Research, Office of Surveillance and Epidemiology, Division of Medication Error Prevention and Analysis (US); 2015 DEC 31. 25 p. OSE RCM No.: 2015-530 and 2015-958.

2 CONCLUSION

The revised Medication Guide (MG), container labels, and carton labeling for Zinbryta are acceptable from a medication error perspective. We note the name [REDACTED] ^{(b) (4)} is currently under objection by the International Nonproprietary Names for Pharmaceutical Substances (INN)³ and therefore, the non-proprietary name must be revised to “daclizumab” throughout all labels and labeling. We note the Office of Biotechnology Products (OBP) reviewer conveyed the following deficiency to the Applicant ⁴“The proper name must be revised to “daclizumab” to comply with 21 CFR 610.60(c) and 21 CFR 610.61(a)” and the Applicant has complied with this request for revision.

We find the Prescribing Information (PI) and Instructions for Use (IFU) unacceptable from a medication error perspective. We identified additional areas of the labeling that can be revised to increase clarity and add important information to mitigate medication errors to promote the safe use of Zinbryta.

We note that the recommended usual dose frequency stated in the PI, [REDACTED] ^{(b) (4)} is inconsistent with the usual dosage statement on the carton labeling, “once monthly” and should be revised to prevent confusion in dosing. We defer to the Division of Neurology Products to determine the appropriate dosing frequency and recommend that all labeling is consistent with the final determination for the recommended dose presentation.

Additionally, we recommend that caregivers be included in the statement “train patients in the proper technique for self-administration” for when patients are unable to self-administer.

Furthermore, we note that previous recommendations for revisions to the Instructions for Use (IFU) have not been implemented. Specifically, we recommended that Step 5 [REDACTED] ^{(b) (4)} include a reminder to the user to refer to Step 3 for proper injection sites, as this would help to prevent patient selection of inappropriate injection sites. We note, however, that the information on proper injection sites is in close proximity to the step with instructions for administering the injection; therefore, we conclude that this revision is not needed, as the

² Abdus-Samad, J. Label and Labeling Review for ZINBRYTA (BLA 761029) Silver Spring (MD): Food and Drug Administration, Center for Drug Evaluation and Research, Office of Biotechnology Products (US); 2016 MAY 12. 13 p.

³ Per Office of Biotechnology Products (OBP), List ^{(b) (4)} of the International Nonproprietary Names for Pharmaceutical Substances (INN), the name [REDACTED] ^{(b) (4)} is currently under objection

⁴ Abdus-Samad, J. Label and Labeling Review for ZINBRYTA (BLA 761029) Silver Spring (MD): Food and Drug Administration, Center for Drug Evaluation and Research, Office of Biotechnology Products (US); 2016 MAY 12. 13 p.

information is readily available. However, the IFU includes a negative statement in Step 6 that reads, “Do not pull back on the plunger” prior to the positive statement “Slowly push the plunger (b) (4) down until the syringe is empty.” We recommend having the positive statement appear prior to the negative statement to minimize the risk of patient misinterpretation of the negative statement. We have shared this recommendation with the Patient Labeling Reviewer for consideration. We provide our recommendations in Section 3 below and advise these are implemented prior to the approval of this BLA.

3 RECOMMENDATIONS FOR THE DIVISION

A. Prescribing Information Highlights

1. The Dosage and Administration Section contains a statement “Train patients in the proper technique for self-administration.” Consider adding “or caregivers” to this statement since some patients may not be able to self-administer their medication. Additionally, this would be consistent with the language in the IFU, i.e. “Before you use the Zinbryta (b) (4) for the first time, your healthcare provider should show you or your caregiver how to prepare and inject your Zinbryta Prefilled Syringe the right way.” Please consider revising the statement to read, “Train patients or caregivers in the proper technique for administration.”
2. We note in the Dosage and Administration Section the (b) (4) (b) (4) is inconsistent with carton labeling of “once a month.” We defer to the Division of Neurology Products to determine the appropriate dosing frequency and recommend that all labeling is consistent with the recommended dose presentation.

B. Full Prescribing Information

1. In Section 2.2 Important Administration Instructions, please consider revising the statement (b) (4) (b) (4) to include caregivers for those patients who may not be able to self-administer their medication and to be consistent with the language in the IFU. We recommend the statement be revised such as, (b) (4) (b) (4)
2. See Above A.2.

C. Instructions for Use:

1. In Step 6 we recommend having the positive statement “Slowly push the plunger (b) (4) down until the syringe is empty” appear prior to the negative statement “Do not pull back on the plunger”, to minimize the risk of patient misinterpretation of the negative statement.

APPENDIX A. LABELS AND LABELING

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/s/

JUSTINE HARRIS
05/20/2016

DANIELLE M HARRIS
05/20/2016

**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medical Policy Initiatives
Division of Medical Policy Programs**

PATIENT LABELING REVIEW

Date: May 18, 2016

To: Billy Dunn, MD
Director
Division of Neurology Products (DNP)

Through: LaShawn Griffiths, MSHS-PH, BSN, RN
Associate Director for Patient Labeling
Division of Medical Policy Programs (DMPP)

Marcia Williams, PhD
Team Leader, Patient Labeling
Division of Medical Policy Programs (DMPP)

Mathilda Fienkeng, PharmD
Team Leader
Office of Prescription Drug Promotion (OPDP)

From: Nyedra W. Booker, PharmD, MPH
Patient Labeling Reviewer
Division of Medical Policy Programs (DMPP)

Aline Moukhtara, RN, MPH
Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

Subject: Review of Patient Labeling: Medication Guide (MG) and
Instructions for Use (IFU)

Drug Name (established name): ZINBRYTA (daclizumab)

Dosage Form and Route: injection, for subcutaneous use

Application Type/Number: BLA 761029

Applicant: Biogen

1 INTRODUCTION

On February 27, 2015 Biogen submitted for the Agency's review an original Biologics Licensing Application (BLA) 761029 for ZINBRYTA (daclizumab) injection, for subcutaneous use. The proposed indication for ZINBRYTA (daclizumab) injection, for subcutaneous use is for:

- The treatment of patients with relapsing forms of multiple sclerosis. Because of its safety profile, the use of ZINBRYTA should generally be reserved for patients who have had an inadequate response to two or more drugs indicated for the treatment of MS.

On April 2, 2015 the Applicant submitted a major amendment to BLA 761029. On August 20, 2015 the Agency granted the Applicant a 3 month review clock extension due to this major amendment submission.

This collaborative review is written by the Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) in response to a request by the Division of Neurology Products (DNP) on March 3, 2015 and March 5, 2015, respectively for DMPP and OPDP to review the Applicant's proposed Medication Guide (MG) and Instructions for Use (IFU) for ZINBRYTA (daclizumab) injection, for subcutaneous use.

DMPP conferred with the Division of Medication Error, Prevention, and Analysis (DMEPA) and a separate DMEPA review of the IFU will be forthcoming.

2 MATERIAL REVIEWED

- Draft ZINBRYTA (daclizumab) injection, for subcutaneous use MG and IFU received on February 27, 2015, and received by DMPP on May 10, 2016.
- Draft ZINBRYTA (daclizumab) injection, for subcutaneous use MG and IFU received on February 27, 2015, and received by OPDP on May 10, 2016.
- Draft ZINBRYTA (daclizumab) injection, for subcutaneous use Prescribing Information (PI) received on February 27, 2015, revised by the Review Division throughout the review cycle, and received by DMPP on May 10, 2016.
- Draft ZINBRYTA (daclizumab) injection, for subcutaneous use Prescribing Information (PI) received on February 27, 2015, revised by the Review Division throughout the review cycle, and received by OPDP on May 10, 2016.

3 REVIEW METHODS

To enhance patient comprehension, materials should be written at a 6th to 8th grade reading level, and have a reading ease score of at least 60%. A reading ease score of 60% corresponds to an 8th grade reading level.

Additionally, in 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. The ASCP and AFB recommended using

fonts such as Verdana, Arial or APHont to make medical information more accessible for patients with vision loss. We have reformatted the MG and IFU documents using the Arial font, size 10 and 11, respectively.

In our collaborative review of the MG and IFU we have:

- simplified wording and clarified concepts where possible
- ensured that the MG and IFU are consistent with the Prescribing Information (PI)
- removed unnecessary or redundant information
- ensured that the MG and IFU are free of promotional language or suggested revisions to ensure that it is free of promotional language
- ensured that the MG meets the Regulations as specified in 21 CFR 208.20
- ensured that the MG and IFU meet the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)

4 CONCLUSIONS

The MG and IFU are acceptable with our recommended changes.

5 RECOMMENDATIONS

- Please send these comments to the Applicant and copy DMPP and OPDP on the correspondence.
- Our collaborative review of the MG and IFU are appended to this memorandum. Consult DMPP and OPDP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the MG and IFU.

Please let us know if you have any questions.

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/s/

NYEDRA W BOOKER
05/18/2016

ALINE M MOUKHTARA
05/18/2016

MARCIA B WILLIAMS
05/19/2016

LASHAWN M GRIFFITHS
05/19/2016

**FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion**

*****Pre-decisional Agency Information*****

Memorandum

Date: May 19, 2016

To: Billy Dunn, M.D., Director
Division of Neurology Products (DNP)

Lawrence Rodichok, M.D., Medical Officer, DNP

Laurie Kelley, PA-C, Regulatory Project Manager, DNP

From: Aline Moukhtara, RN, MPH, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: Mathilda Fienkeng, PharmD, Team Leader, OPDP

Subject: OPDP Comments on proposed labeling for
ZINBRYTA (daclizumab) injection, for subcutaneous use
BLA 761029

On March 5, 2015, DNP consulted OPDP to review the draft Prescribing Information (PI), Medication Guide, Instructions for Use (IFU), and carton and container labeling for ZINBRYTA (daclizumab) injection, for subcutaneous use (Zinbryta).

PI

OPDP's review of the proposed PI is based on the substantially complete version of the PI titled "FDA Comments 16May2016.doc," and obtained from DNP SharePoint on May 17, 2016. OPDP's comments on the draft PI are provided below.

Medication Guide and IFU

A combined OPDP and Division of Medical Policy Programs (DMPP) patient labeling review was conducted, and comments on the Medication Guide and IFU were sent under a separate cover by DMPP on May 19, 2016.

Carton and Container Labeling

OPDP comments on the proposed carton and container labeling will be provided under a separate cover.

If you have any questions, please contact Aline Moukhtara at (301) 796-2841 or Aline.Moukhtara@fda.hhs.gov.

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/s/

ALINE M MOUKHTARA
05/19/2016



Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Biotechnology Products

LABEL AND LABELING REVIEW

Date:	May 12, 2015
Reviewer:	Jibril Abdus-Samad, PharmD, Labeling Reviewer Office of Biotechnology Products Jibril Abdus-samad -S <small>Digitally signed by Jibril Abdus-samad -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=1300433429, cn=Jibril Abdus-samad -S Date: 2016.05.12 15:08:43 -0400</small>
Through:	Chen Sun, MD, PhD, Quality Reviewer Division of Biotechnology Review and Research II Chen Sun -S <small>Digitally signed by Chen Sun -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Chen Sun -S, 0.9.2342.19200300.100.1.1=0010409028 Date: 2016.05.12 15:38:55 -0400</small>
Application:	BLA 761029/0
Product:	Zinbryta (daclizumab)*
Applicant:	Biogen Inc.
Submission Dates:	February 27; September 10 2015; March 18 2016

Executive Summary:

The container label and carton labeling for Zinbryta (daclizumab) were reviewed and found to comply with United States Pharmacopeia (USP), [USP 38/NF 33 December 1, 2015 to April 30, 2016] and the following regulations: 21 CFR 610.60 through 21 CFR 610.67; 21 CFR 201.2, 21 CFR 201.6 through 21 CFR 201.25; 21 CFR 201.51, and 21 CFR 201.57. However the following deficiencies are unresolved:

- The proper name must be revised to "daclizumab" to comply with 21 CFR 610.60(c) and 21 CFR 610.61(a)
- The dosing frequency must be updated to comply with 21 CFR 201.5(c), 21 CFR 201.50, and 21 CFR 201.100(b)2.

The container label and carton labeling submitted on March 18, 2016 are unacceptable.

Background and Summary Description:

The Applicant submitted BLA 761029 Zinbryta (daclizumab) on February 27, 2015. Table 1 lists the proposed characteristics of Zinbryta (daclizumab).*

* For purposes of this review, we refer to the proposed product as "daclizumab." The Applicant proposed (b) (4) which FDA objected to in list (b) (4) of the International Nonproprietary Names for Pharmaceutical Substances.

Table 1: Proposed Product Characteristics of Zinbryta (daclizumab).

Proprietary Name:	Zinbryta
Proper Name:	daclizumab
Indication:	treatment of patients with relapsing forms of multiple sclerosis
Dose:	150 mg subcutaneously once a month
Route of Administration:	subcutaneous injection
Dosage Form:	Injection
Strength and Container-Closure:	150 mg/mL single-dose prefilled syringe
Storage and Handling:	<ul style="list-style-type: none"> • Store in refrigerator between 2°C to 8°C (36°F to 46°F). Do not freeze. • Once removed from the refrigerator, ZINBRYTA should be allowed to warm to room temperature (about 30 minutes) prior to injection. Do not use external heat sources such as hot water to warm ZINBRYTA. • If refrigeration is unavailable, ZINBRYTA may be stored up to 30°C (86°F) for a period up to 30 days, protected from light. Do not place ZINBRYTA back into the refrigerator after warming to room temperature. If ZINBRYTA is at room temperature (up to 30°C/86°F) for more than 30 days, it should be discarded.

Materials Reviewed:

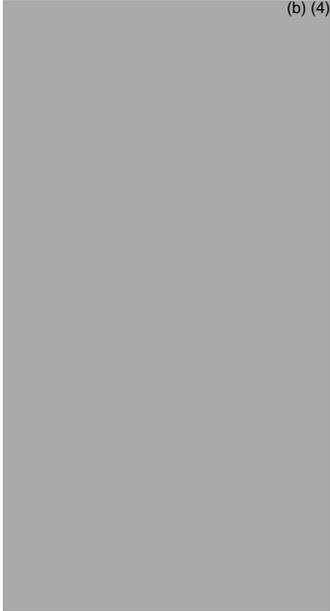
- Container Label (trade (b) (4))
- Carton Labeling (trade (b) (4))

Start of Sponsor Material

Container Labels

trade

(b) (4)



End of Sponsor Material

Subpart G-Labeling Standards
Subpart A-General Labeling Provisions

I. Container

A. 21 CFR 610.60 Container Label

(a) Full label. The following items shall appear on the label affixed to each container of a product capable of bearing a full label; *not applicable. See (c) Partial Label.*

(b) Package label information. If the container is not enclosed in a package, all the items required for a package label shall appear on the container label; *not applicable.*

(c) Partial label. If the container is capable of bearing only a partial label, the container shall show as a minimum

- The name (expressed either as the proper or common name); *does not conform.*

OBP Request:

In list (b) (4) of the International Nonproprietary Names for Pharmaceutical Substances (INN), the name (b) (4) is currently under objection. Revise your labeling to use the nonproprietary name "daclizumab". *The Applicant has not revised. Revision is still pending.*

Relocate the proper name "daclizumab" to appear under the proprietary name. This is the appropriate display of for CDER-regulated biological products. *Applicant revised the position of the proper name as requested. However, the actual proper name still requires revisions as detailed above.*

- The lot number or other lot identification; *conforms.*
- The name of the manufacturer; *conforms.*
- In addition, for multiple dose containers, the recommended individual dose; *not applicable. Zinbryta is packaged in a single-dose PFS.*
- Containers bearing partial labels shall be placed in a package which bears all the items required for a package label; *conforms.*

(d) No container label. If the container is incapable of bearing any label, the items required for a container label may be omitted, provided the container is placed in a package which bears all the items required for a package label. *Not applicable.*

(e) Visual inspection. When the label has been affixed to the container, a sufficient area of the container shall remain uncovered for its full length or circumference to permit inspection of the contents; *insufficient data to support.*

OBP Request: Indicate how the label is affixed to the vial and where the visual area of inspection is located per 21 CFR 610.60(e). *The Applicant provided a photo that illustrate there is adequate visual areas for inspections.*

B. 21 CFR 201.2 Drugs and devices; National Drug Code numbers – The National Drug Code (NDC) number is located at the top of the label. [See 21 CFR 207.35]; *not applicable for a partial label. NDC appears on carton labeling.*

- C. 21 CFR 201.5 Drugs; adequate directions for use; *conforms*.
- D. 21 CFR 201.6 Drugs; misleading statements; *conforms*.
- E. 21CFR 201.10 Drugs; statement of ingredients; placement and prominence; *conforms*. *The inactive ingredients appear on the carton labeling.*
- F. 21 CFR 201.15 Drugs; prominence of required label statements; *does not conform*.

We consider the vial container label a partial label due to its small size per 21 CFR 610.60(c). Therefore we provided recommendations to preserve the required and recommended information on the label and remove less important information to provide more white space and improve readability.

OBP Request: Add the route of administration "For Subcutaneous Use Only". To make room consider the following (in order of preference):

- Delete distributor from the partial label as this is not required or revise to read "Distr: AbbVie, Inc".
- Revise the manufacturer information to read "Mfd by: Biogen Inc."
- Delete the dosage form "Injection".

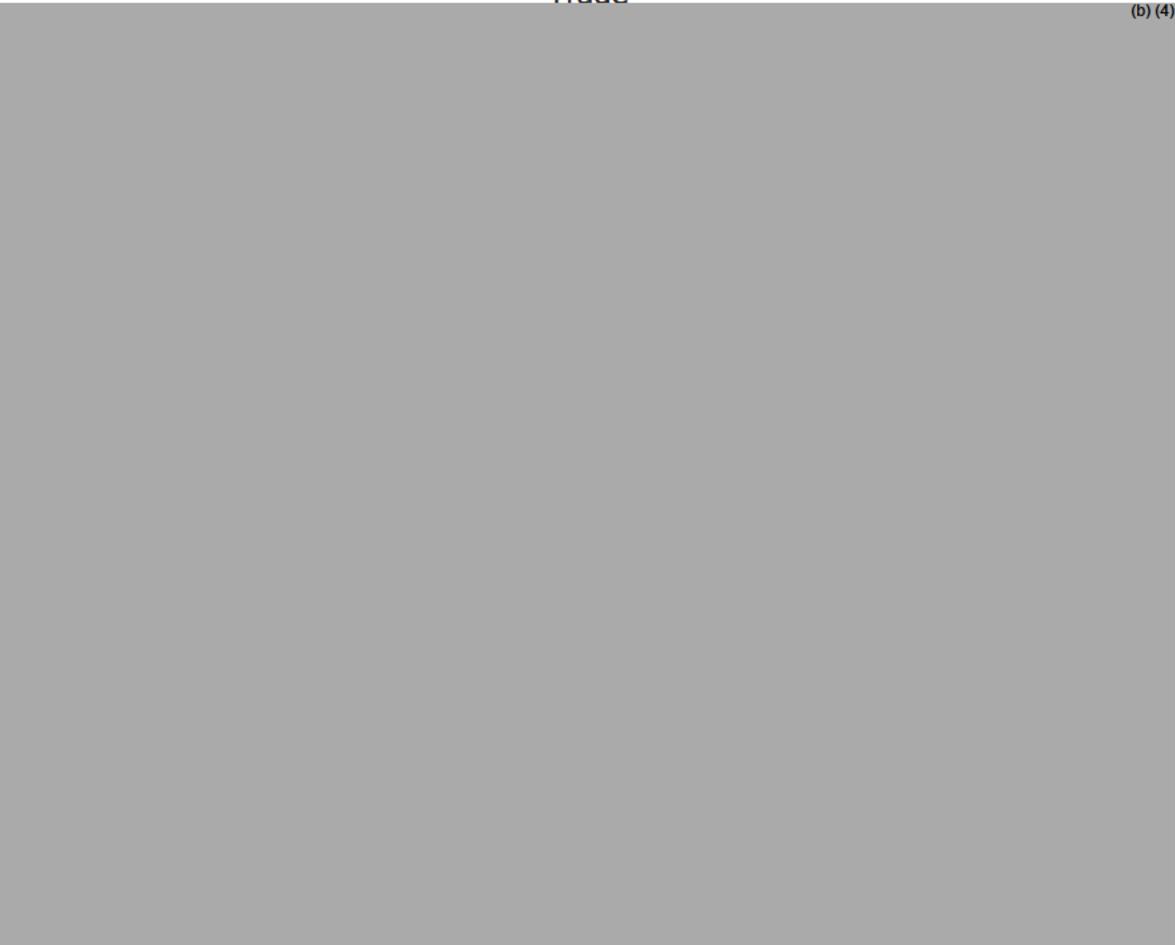
Applicant revised as requested.

- G. 21 CFR 201.17 Drugs; location of expiration date; *conforms*.
- H. 21 CFR 201.25 Bar code; *conforms*.
- I. 21 CFR 201.50 Statement of identity; *conforms*.
- J. 21 CFR 201.51 Declaration of net quantity of contents; *conforms*.
- K. 21 CFR 201.55 Statement of dosage; *conforms*.
- L. 21 CFR 201.100 Prescription drugs for human use; *conforms*. *Required items appear on the carton labeling.*

Start of Sponsor Material

Carton Labeling
Trade

(b) (4)



End of Sponsor Material

II. Carton

A. 21 CFR 610.61 Package Label:

a) The proper name of the product; [see 21 CFR 600.3 (k) and section 351 of the PHS Act]; *does not conform*.

OBP Request:

In list (b) (4) of the International Nonproprietary Names for Pharmaceutical Substances (INN), the name (b) (4) is currently under objection. Revise your labeling to use the nonproprietary name "daclizumab". *The Applicant has not revised. Revision is still pending.*

b) The name, addresses, and license number of manufacturer; *conforms*.

c) The lot number or other lot identification; *conforms*.

- d) The expiration date; *conforms*.
- e) The preservative used and its concentration, if no preservative is used and the absence of a preservative is a safety factor, the words "no preservative"; *conforms*.
- f) The number of containers, if more than one; *not applicable*.
- g) The amount of product in the container expressed as (1) the number of doses, (2) the volume, (3) units of potency, (4) weight, (5) equivalent volume (for dried product to be reconstituted), or (6) such combination of the foregoing as needed for an accurate description of the contents, whichever is applicable; *conforms*.
- h) The recommended storage temperature; *does not conform*.
The carton labeling does not display the storage instructions outside of the refrigerator that appear in the prescribing information section 16.

OBP Request: Add the storage instructions outside the refrigerator that appear in the PI. We find the instructions should clearly designate (b) (4) patient storage. For example:

(b) (4) Store in a refrigerator between 2°C to 8°C (36°F to 46°F) in original carton to protect from light. Do not freeze. (b) (4)



Applicant revised as requested.

- i) The words "Do not Freeze" or the equivalent, as well as other instructions, when indicated by the character of the product; **does not conform. We requested the addition of "Do not Shake" in the request above. Applicant revised as requested.**
- j) The recommended individual dose if the enclosed container(s) is a multiple-dose container; *not applicable.*
- k) The route of administration recommended, or reference to such directions in and enclosed circular; *conforms.*
- l) Known sensitizing substances, or reference to enclosed circular containing appropriate information; *not applicable.*
- m) The type and calculated amount of antibiotics added during manufacture; *not applicable.*
- n) The inactive ingredients when a safety factor, or reference to enclosed circular containing appropriate information; *not applicable.*
- o) The adjuvant, if present; *not applicable.*
- p) The source of the product when a factor in safe administration; *not applicable.*
- q) The identity of each microorganism used in manufacture, and, where applicable, the production medium and the method of inactivation, or reference to an enclosed circular containing appropriate information; *not applicable.*
- r) Minimum potency of product expressed in terms of official standard of potency or, if potency is a factor and no U.S. standard of potency has been prescribed, the words "No U.S. standard of potency"; **does not conform.**

OBP Request: Add the statement "No U.S. standard of potency" on the rear panel to comply with 21 CFR 610.61(r).
Applicant revised as requested.

s) The statement "Rx only" for prescription biologicals; *conforms*.

- Note: If product has a medication guide, a statement is required on the package label if it is not on the container label (see above). It is recommended on both labels; *conforms*. However it appears on the carton labeling only due to the small size of the PFS container label.

B. 21 CFR 610.62 Proper name; package label; legible type [Note: Per 21 CFR 601.2(c)(1), certain regulation including 21 CFR 610.62 do not apply to the four categories of "specified" biological products listed in 21 CFR 601.2(a)]. *Exempt. Zinbryta (daclizumab) is a monoclonal antibody, therefore a specified biological product.*

C. 21 CFR 610.63 Divided manufacturing responsibility to be shown; *not applicable*.

D. 21 CFR 610.64 Name and address of distributor; *conforms*.

The name and address of the distributor of a product may appear on the label provided that the name, address, and license number of the manufacturer also appears on the label and the name of the distributor is qualified by one of the following phrases: "Manufactured for _____". "Distributed by _____", "Manufactured by _____ for _____", "Manufactured for _____ by _____", "Distributor: _____", or "Marketed by _____". The qualifying phrases may be abbreviated.

E. 21 CFR 610.67 Bar code label requirements; *conforms*.

Biological products must comply with the bar code requirements at §201.25 of this chapter;

F. 21 CFR 201.2 Drugs and devices; National Drug Code numbers – The National Drug Code (NDC) number is located on top of the label [See 21 CFR 207.35]; *conforms*.

G. 21 CFR 201.5 Drugs; adequate directions for use; *does not conform*.

OBP Request: Revise the dosage frequency that appears on the principal display panel and Usual Dosage statement on the rear panel from "once a month" to "once every 4 weeks". *The Applicant has not revised. Revision is still pending as the Division of Neurology Products to determine the appropriate dosing frequency.*

H. 21 CFR 201.6 Drugs; misleading statements; *conforms*.

I. 21 CFR 201.10 Drugs; statement of ingredients [Placement and Prominence]; *conforms*.

J. 21 CFR 201.15 Drugs; prominence of required label statements; *does not conform*.

OBP Requests:

Increase the prominence of the strength "150 mg/mL" and the route of administration "For Subcutaneous Use Only". *Applicant revised as requested.*

Decrease the prominence of the following by removing the bolding: "see package insert for dosage and administration" and "Rx only". *Applicant revised as requested.*

K. 21 CFR 201.17 Drugs; location of expiration date; *conforms*.

L. 21 CFR 201.25 Bar code label requirements; *conforms*.

M. 21 CFR 201.50 Statement of identity; *conforms*.

N. 21 CFR 201.51 Declaration of net quantity of contents; *conforms*.

O. 21 CFR 201.55 Statement of dosage; *does not conform (See below)*.

P. 21 CFR 201.100 Prescription drugs for human use; *does not conform*.

OBP Requests:

Revise the dosage frequency that appears on the principal display panel and Usual Dosage statement on the rear panel from "once a month" to "once every 4 weeks". *The Applicant has not revised. Revision is still pending as the Division of Neurology Products determines the appropriate dosing frequency.*

OBP Request: Revise the list of ingredients to comply with USP General Chapters <1091> Labeling of Inactive Ingredients. For example:

Each 1 mL single-dose prefilled syringe delivers daclizumab 150 mg, polysorbate 80, USP (0.3 mg), sodium chloride (5.84 mg) sodium succinate, anhydrous (5.94 mg), succinic acid (b) (4) (0.35 mg), and Water for Injection, USP.

Applicant revised as requested.

Review issues

This section described additional labeling issues

Nonproprietary Name

The Applicant has submitted a request to the World Health Organization (WHO) to uniquely identify DAC HYP using the existing INN (b) (4). However, FDA objected to (b) (4) in list (b) (4) of the International Nonproprietary Names for Pharmaceutical Substances. Therefore we recommended the Applicant revise the proper name to “daclizumab” on all labels and labeling.

(b) (4)
On March 18, 2016 submission, the Applicant withdrew their (b) (4) configuration as they determined it would no longer be needed.

Conclusions:

The container label and carton labeling for Zinbryta (daclizumab) were reviewed and found to comply with United States Pharmacopeia (USP), [USP 38/NF 33 December 1, 2015 to April 30, 2016] and the following regulations: 21 CFR 610.60 through 21 CFR 610.67; 21 CFR 201.2, 21 CFR 201.6 through 21 CFR 201.25; 21 CFR 201.51, and 21 CFR 201.57. However, the following deficiencies are unresolved:

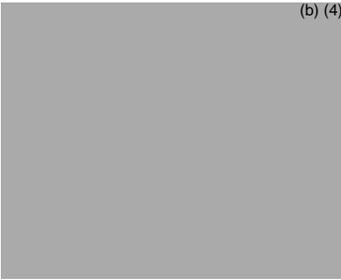
- The proper name must be revised to “daclizumab” to comply with 21 CFR 610.60(c) and 21 CFR 610.61(a)
- The dosing frequency must be updated to comply with 21 CFR 201.5(c), 21 CFR 201.50, and 21 CFR 201.100(b)2.

The container labels and carton labeling submitted on March 18, 2016 are unacceptable (see below). The proper name deficiencies are highlighted in the red circles. The dosing frequency deficiencies are highlighted in the green circles.

Container Label

[\\cdsesub1\evsprod\bla761029\0068\m1\us\draft-pfs-syringe-label.pdf](#)

(b) (4)



Carton Labeling

[\\cdsesub1\evsprod\bla761029\0068\m1\us\draft-pfs-pack-carton.pdf](#)

(b) (4)





Division of Pediatric and Maternal Health
Office of New Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Silver Spring, MD 20993
Tel 301-796-2200
FAX 301-796-9744

**DIVISION OF PEDIATRIC AND MATERNAL HEALTH,
MATERNAL HEALTH TEAM REVIEW**

Date: 4-21-2016

From: Leyla Sahin, M.D.
Medical Officer, Maternal Health Team
Division of Pediatric and Maternal Health

Through: Tamara Johnson, M.D., M.S.
Team Leader, Maternal Health Team
Division of Pediatric and Maternal Health

Lynne P. Yao, M.D.
Director,
Division of Pediatric and Maternal Health

To: Division of Neurology Products

Drug: Zinbryta (dacluzimab) injection for subcutaneous use; BLA 761029

Subject: Post-marketing requirement language for a pregnancy registry

Applicant: Biogen

Materials Reviewed: • Applicant's proposed labeling
• BLA submission documents

Consult Question: Please assist with language for a postmarketing requirement for a pregnancy registry

INTRODUCTION

The applicant submitted a new biologics license application (BLA) on February 27, 2015, for Zinbryta (daclizumab) 150 mg/mL single-dose prefilled syringe for subcutaneous use, with a proposed indication for the treatment of adult patients with relapsing forms of multiple sclerosis (MS).

The Division of Neurology Products (DNP) consulted the Division of Pediatric and Maternal Health (DPMH) on March 21, 2016, for input on language for a postmarketing requirement for a pregnancy registry.

BACKGROUND

Product background

Daclizumab high yield process (DAC HYP) is a recombinant humanized immunoglobulin G1 (IgG1) monoclonal antibody that binds specifically to the alpha subunit of the interleukin-2 receptor (IL-2R α , CD25). The precise mechanism by which daclizumab exerts therapeutic effects in multiple sclerosis is unknown, but is presumed to involve modulation of IL-2 signaling by selectively blocking CD25. This product is not approved anywhere in the world. A related product, daclizumab Nutley (Zenapax®, BLA 103749), was approved on December 10, 1997, for prophylaxis of acute organ rejection in adults and pediatric patients 11 month of age and older receiving renal transplants. Daclizumab Nutley is a different formulation and uses a different manufacturing process than DAC HYP. Zenapax was withdrawn from the market in 2012 due to low usage.¹

On August 20, 2015 the BLA's PDUFA goal date was extended due to a major amendment related to submission of additional safety data.

Because of liver toxicity safety issues, the Indications and Use of daclizumab will be labeled as "reserved for patients who have had an inadequate response to two or more drugs indicated for the treatment of MS". Daclizumab will be available only through a restricted distribution program under a risk evaluation and mitigation strategy (REMS).

Disease background

Relapsing multiple sclerosis is an immune mediated chronic inflammatory disease that is more common in women than in men. With a typical age of onset in the third decade, it is a common disease in females of reproductive potential and in pregnant women.²

¹ Dr. Maria Lourdes Villalba's Clinical review in DARRTS 3-24-2016

² Karp I, Manganas A, Sylvestre MP, et al. Does pregnancy alter the long-term course of multiple sclerosis? *Annals of Epidemiology* 24(2014):504-508.

DISCUSSION

Pregnancy Safety Data

Nonclinical data in the current working version of labeling include an increase in embryo-fetal death in monkeys administered doses greater than 30 times the recommended human dose based on AUC.

A search of published literature was performed and no reports on the safety of daclizumab in pregnancy were found. The applicant's review of pregnancy cases from their safety database (as of August 8, 2014), based on pregnancies that occurred during the clinical development program, includes the following:

	DAC HYP*	Interferon β -1a	Placebo
Total number of pregnancies	37	18	1
Live birth	15	8	0
Spontaneous abortion	4	1	1
Elective termination	5	3	0
Ectopic pregnancy	2	3	0
Lost to follow up	2	1	0
Outcome pending	7	2	0

*On DAC HYP or ≤ 6 months after final dose ($t_{1/2} = 21$ days)

There was one reported congenital heart defect reported in the infant of a woman who had discontinued daclizumab 3 months before the pregnancy and was treated with interferon in the first month of pregnancy. There were no reported congenital anomalies in the interferon group.

Post-marketing requirement (PMR) language for a pregnancy registry

Available data are limited and insufficient to inform the safety of daclizumab exposure in pregnancy. Therefore DNP plans to issue a pregnancy registry PMR with the following proposed language:

“A prospective, registry-based observational exposure cohort study conducted in the United States that compares the maternal, fetal, and infant outcomes of women with multiple sclerosis exposed to Zinbryta (daclizumab) during pregnancy to unexposed control populations (one with women with multiple sclerosis who have not been exposed to Zinbryta (daclizumab) in pregnancy and the other in women without multiple sclerosis). The registry will detect and record major and minor congenital malformations, spontaneous abortions, stillbirths, elective terminations, and any other adverse pregnancy outcomes. These outcomes will be assessed throughout pregnancy. Infant outcomes, including effects on postnatal growth and development, will be assessed through at least the first year of life.”

CONCLUSION

DPMH concurs with DNP's proposed PMR language. The applicant has completed pregnancy registries for two MS products, Tysabri (natalizumab) and Avonex (interferon β -1a) and currently has an ongoing multiproduct pregnancy registry for two other MS products, Tecfidera (dimethyl fumarate) and Plegridy (peg interferon beta-1a). Zinbryta can be added to their multiproduct MS pregnancy registry to leverage existing infrastructure and resources.

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

/s/

LEYLA SAHIN
04/21/2016

TAMARA N JOHNSON
04/22/2016

LYNNE P YAO
04/22/2016

DEPARTMENT OF HEALTH & HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Devices and Radiological Health
Office of Compliance, Division of Manufacturing & Quality
Respiratory, Ear/Nose/Throat, General Hospital, and Ophthalmic Devices Branch

Date: March 31, 2016

To: Laurie Kelly, Sr. Program Manager, OMPT/CDER/OND/ODEI/DNP, WO22
RM 4380, Laurie.Kelley@fda.hhs.gov

John Marler, MD., OMPT/CDER/OND/ODEI/DNP, WO22/RM 4340,
John.Marler@fda.hhs.gov

Office of combination products at combination@fda.gov

Through: LT Viky Verna, Combination Product Branch Lead, Senior Regulatory
Officer, REGO, DMQ, OC, CDRH, WO-66, Room 3435

Viky Verna -S
Digitally signed by Viky Verna -S
DN: c=US, o=U.S. Government, ou=HHS,
ou=FDA, ou=People, cn=Viky Verna -S,
0.9.2342.19200300.100.1.1-2000495623
Date: 2016.04.04 10:29:46 -04'00'

From: Christopher J Brown, P.E. , REGO, DMQ, OC, CDRH, WO-66, Room 3428

Applicant: Biogen Idec, Inc.
225 Binney Street,
Cambridge, Massachusetts, 02142-1453, United States
FEI #: 1220951

Application # BLA 761029

Consult # ICC1500646

Product Name: Daclizumab (PFS)

Pre-Approval Inspection: No

Documentation Review: No Additional Information Required

Final Recommendation: APPROVAL

The Office of Compliance at CDRH received a consult request from CDER to evaluate the applicant's compliance with applicable Quality System Requirements for the approvability of BLA 7601029.

PRODUCT DESCRIPTION

Daclizumab will be marketed in a manual prefilled syringe configuration. The PFS container closure system consists of a (b) (4) 1 mL long fixed needle syringe (b) (4) utilizing USP/Ph. Eur Type I (b) (4) glass. Each syringe contains an embedded staked 0.5 inch long, 29 gauge (b) (4) (b) (4), 5 bevel needle for subcutaneous injection, a (b) (4) rubber plunger stopper, and a rigid needle shield (RNS) (b) (4) (b) (4). The (b) (4) components (plunger stopper and RNS) are not made with natural rubber latex (b) (4)



Figure 1. DAC HYP Pre-filled Syringe Commercial Finished Goods Packaging

The DAC HYP pre-filled syringe (PFS) drug product is manufactured at the (b) (4) facility (b) (4) Table 1 shows the manufacturer for the combination product, suppliers, and firms that provide support activities.

Table 1. Manufacturers and suppliers.

Company	Location	Function	Facility Establishment Identifier
(b) (4)			

REGULATORY HISTORY

The following facilities were identified as being subject to applicable Quality System Requirements under 21 CFR part 820:

1. Biogen Idec, Inc.
10/12/14/15 Cambridge Center, 225/301 Binney Street,
Cambridge, Massachusetts, 02142-1453, United States
FEI #: 1220951

Responsibility – Applicant transferred product to Biogen Idec Inc. Firm’s Corporate Headquarters, owner of combination product. Owner has responsibility for the product and related regulator documents.

Inspectional History - An analysis of the firm’s inspection history over the past 2 years showed that inspections were conducted on: 06/22/2015-06/26/2015, and 06/24/2014-07/03/2014. The 2014 and 2015 inspection covered drug GMP and was classified VAI.

Inspection Recommendation:

An inspection is not required because:

- A recent inspection of the firm was acceptable.

NOTE: The firm is responsible for activities related to the manufacturing and development of the final combination product therefore the next inspection at the firm should cover compliance with applicable Quality System (QS – 21 CFR 820) requirements. (See Inspectional Guidance at the end).

2. [REDACTED] (b) (4)
FEI # [REDACTED] (b) (4)

Responsibility – The firm manufactures the combination product and performs the following duties; drug product manufacturing, [REDACTED] (b) (4) testing, quality control testing, and visual inspection. As the manufacturer of the combination product, the firm is subject to QS regulations and associated inspections.

Inspectional History – An analysis of the firm’s inspection history over the past 2 years showed that inspections were conducted on: [REDACTED] (b) (4). The inspections covered drug GMP. The [REDACTED] (b) (4) inspection was classified as VAI, and the [REDACTED] (b) (4) was classified NAI.

Inspection Recommendation:

An inspection is not required because:

- A recent inspection of the firm was acceptable.

NOTE: The firm is responsible for activities related to the manufacturing and development of the final combination product therefore the next inspection at the firm should cover compliance with applicable Quality System (QS – 21 CFR 820) requirements. (See Inspectional Guidance at the end).

DOCUMENTATION REVIEW

The application was searched for documents pertaining to applicable 21 CFR part 820 regulations for this combination product.

The firm provided an outline of the quality systems for the DAC HYP pre-filled syringe (PFS) drug product. They stated that in the event that there are changes which have a minimal potential to have an adverse effect on product quality, these will be reported in an annual report, consistent with the recommendations in current FDA guidances for postapproval changes. All other future changes to the combination product will be assessed in accordance with the recommendations

in current FDA guidances related to submissions for postapproval modifications to a combination product approved under a BLA.

The DAC HYP PFS container closure system is manufactured (b) (4)
(refer to Section 3.2.P.3.3.1; Description of Manufacturing Process and Process Controls – Manufacturing Description). (b) (4)
(refer to Section 3.2.P.3.3.2; Description of Manufacturing Process and Process Controls – Packaging Information for Finished Product).

Biogen Idec states that they are responsible for providing technical and quality oversight of the contract manufacturing organizations (CMOs) responsible for drug product manufacture and secondary packaging activities, and subsequently any companies utilized by the CMOs to manufacture and supply components of the PFS container closure system. The requirements for oversight of the CMOs are governed by Biogen Idec procedures GLOBL-24525 Contract Manufacturing Organization (CMO) Management and GLOBL-24472 Quality Agreements. These governing procedures are supported by the CMO's internal procedures.

Biogen Idec states that Quality Management System is based on GLOBL-1001 Biogen Idec Quality Manual. The development of a new medical device or combination product, or improvements to these products, is managed to achieve compliance with the applicable regulatory and international standards requirements. This development is governed according to the following Biogen Idec internal procedures:

- GLOBL-25612 Medical Devices/Combination Products
- GLOBL-24131 Risk Management
- GLOBL-10080 Change Management
- GLOBL-24504 Corrective Action and Preventative Action (CAPA)

Management Control, 21 CFR 820.20

The firm provided a summary of the management controls. The statements below outline the Company's management responsibilities under the Quality Management System:

- Management with executive responsibility is defined, and their responsibilities to determine, communicate, and designate the appropriate authority throughout the quality system organization are detailed within GLOBL-23809 Management and Quality Responsibilities for the Quality Management Systems.
- Management's intentions and directions with respect to quality are described within GLOBL-4559, Quality Policy.
- Management with executive responsibility ensures that the quality policy and objectives are met, and the quality plan outlined, within the organization through the establishment, maintenance, and improvement of the Quality Management System.

The firm stated that the Quality Manual provides the organizational structure of the processes and documentation established and maintained to ensure all practices, resources, and activities supporting product design and production meet regulatory requirements and are performed under proper control. This information is outlined in GLOBL-1001, Quality Manual. The continued suitability and performance of the quality system is monitored and reported on through

Management Review as detailed in PRCD-23812, Management Review.

Per the firm, the following documents outline the drug product manufacturer's (b) (4) Quality Management System for Management Responsibility:

- The management responsibilities are described in the Quality Management Manual, (b) (4) SOP 11935 Manual of Quality Management. This SOP also includes management reviews according to (b) (4) SOP 11921 Quality Management Review to check the process performance, product quality, and quality systems.

Per the firm, the following documents outline the secondary packaging sites' (b) (4) Quality Management Systems for Management Responsibility:

- The (b) (4) management responsibilities are described in the (b) (4) SOP 211.22 Responsibilities of the Quality Unit. This SOP also includes management reviews according to (b) (4) SOP 211.192.a Quality Management Review to check the process performance, product quality, and quality systems.
- The (b) (4) management responsibilities are described in the (b) (4) SOP C-QA-019 Roles and Responsibilities of the Quality Unit. This SOP also includes management reviews according to (b) (4) SOP C-QA-080 Management Review to check the process performance, product quality, and quality systems.

The information provided by the firm has adequately addressed the requirements of 21 CFR 820.20.

Design Control, General, 21 CFR 820.30

The firm states that when developing a new product or product enhancements, they manage the development activities to achieve compliance with international standards and regulatory and project requirements. Design planning, the recording and maintenance of design input and output, design reviews, verification, validation, changes, and transfer activities are captured in the Company's quality system. The following Biogen Idec procedure outlines the design control process:

- PRCD-26136 Design Control Procedure

The combination of Supplier activities and Company activities constitute the design control for the product.

Design and Development Planning, General, 820.30(b)

Per the firm, design and development planning is performed in accordance with PRCD-26136 Design Control Procedure. Additionally, (b) (4) procedure SOP 10983, Project Realization Regarding Packaging Material Development describes the project management procedure.

Design Inputs, General, 820.30(c)

Per the firm, design inputs are captured in accordance with PRCD-26136 Design Control Procedure. The firm provided a full list of the design inputs patient population, functional and performance requirements interface requirement, biocompatibility, environmental, safety, sterility, labeling and packaging.

Design Outputs, General, 820.30(d)

Per the firm, the design outputs are documented within the Company's quality system in accordance with PRCD-26136 Design Control Procedure. The firm provided a detailed description and specifications for the combination product. The firm provided the list of applicable standards for the product.

Design Review, 820.30(e)

The firm states that they provide technical and quality oversight of drug product and secondary packaging manufacturing activities per GBLB-24525 Contract Manufacturing Organization (CMO). Management is directly involved in reviewing the design output and consequent verification activities to ensure compliance to Company and regulatory requirements.

Additionally, the firm states that they perform stage-appropriate Design Reviews in accordance with PRCD-26136 Design Control Procedure.

Design Verification, 820.30(f)

The firm states that the design outputs are verified against the design input requirements through verification of component supplier documentation and verification through testing in accordance with PRCD-26136 Design Control Procedure.

Per the firm, design verification was performed to confirm that the design inputs met the required design outputs. Biological evaluation and functionality were conducted on the proposed commercial, PFS. Design verification testing was also performed using relevant sections of recognized national and international standards. The firm provided the input requirement, verification/acceptance criteria, and rationale for the criteria and test.

Design Validation, 820.30(g)

Per the firm, the design validation was performed to ensure that the design output is safe and effective in the intended use setting. The validation was accomplished through a human factors program to ensure that the system is able to meet the intended use according to Biogen Idec procedures. PRCD-32565 Application of Human Factors and Usability Engineering, as well as through clinical experience of the PFS container closure system, refer to the human factors evaluation.

To confirm that the DAC HYP 150 mg/mL formulation would remain compatible with the chosen PFS and not impede the functionality of the syringe with storage, the plunger break loose force, plunger glide force, and needle shield removal force were measured and data was provided for up to 36 months of storage at 2-8°C, up to 6 months of storage at 25°C, and up to 4 months of storage at 40°C. Testing was performed on two drug product lots produced at (b) (4) an engineering run (Lot VVJB08) and a clinical lot (Lot VVLF85). The two lots were manufactured using different (b) (4) PFS lots. Prior to testing, the syringes were equilibrated (b) (4) (b) (4) A total of 20 syringes were tested for both drug product lots for plunger break loose and glide forces.

(b) (4)
(b) (4) The firm provided data from a number of shipping validation tests designed to confirm the robustness of the shipping container and the method of transport and

demonstrate that the product temperature is maintained and package integrity is preserved.

Design Transfer, 820.30(h)

The states that they provide oversight to transfer activities to ensure that the appropriate design outputs and production specification procedures have been completed, reviewed, and approved.

Per the firm, the procedures governing the design transfer activities include:

- Biogen Idec procedure on Change Control, GLOBL-10080 Change Management
- The technology transfer into (b) (4) manufacturing, the product and process development, and the validation processes for the area of the primary pharmaceutical process (b) (4) is regulated by (b) (4) SOP 11404 Process Development and Validation.
- (b) (4) SOP 211.68.a.1 Equipment Installation and Operation Qualification
- (b) (4) SOP 211.68.a.1.a Process Operation and Performance Qualification
- (b) (4) SOP C-VAL-003 Validation Master Plan

Design Changes, General, 820.30(i)

The firm states that design and development changes are identified and documented. The changes are reviewed, verified, and validated, where appropriate, and approved before implementation in accordance with Biogen Idec procedure, GLOBL-10080 Change Management. The Supplier Quality/Supply Agreement with each Component Manufacturer specifies that the Component Manufacturer is responsible for the design changes for each Component. The Component Manufacturer is accountable to communicate design changes to the responsible CMO prior to implementation. The CMO further communicates the design changes to the Company as described per terms of the respective Quality Agreement.

The procedures within the CMO Quality Systems that are used for the controlling of Component changes are provided in:

- CMO procedures on Change Control, (b) (4) SOP 10411 Change Control System, (b) (4) Change Control PCI 211.100.a.5 Change Control Process, and (b) (4) (b) (4) SOP C-QA-007 Change Control Procedure.

Design History File § 820.30 (j)

Per the firm, their design history file contains and/or references the records (including CMO and/or Component Manufacturer records) necessary to demonstrate that the design was developed in accordance with the approved design plan and PRCD-26136 Design Control Procedure.

The firm did not provide a copy or a summary of the specific plan used to design the combination product. However, considering the risk, the inspectional history and details provided on the design (inputs, outputs, validation and verification), additional information can be collected, and reviewed for adequacy at the next routine medical device inspection.

The information provided by the firm has adequately addressed the requirements of 21 CFR 820.30.

Purchasing Controls, 21 CFR 820.50

The firm stated that the Company ensures control through purchasing processes, supplier selection and evaluation, material receipt, and control. These processes are managed according to the procedures below:

- GLBL-24239 Supplier Management
- GLBL-24525 Contract Manufacturing Organization (CMO) Management
- GLBL-24472 Quality Agreement

Per the firm, these governing procedures are supported by CMO internal procedures:

- (b) (4) SOP 10101 Qualification of Suppliers, Contract Laboratories and Service Providers (describes the qualification of suppliers, contract laboratories, and service providers)
- (b) (4) SOP 211.80.a.15, Vendor Selection
- (b) (4) SOP C-QA-012, Vendor Audit Program

Per the firm, the list of the approved suppliers is maintained by the CMOs. The specifications agreed with the suppliers are recorded in inspection plans that are described below:

- (b) (4) SOP 20055 Test Planning and Administration of Test Orders in SAP/QM
- (b) (4) SOP 10871 System of Incoming-Goods Inspection of Packaging Materials
- (b) (4) SOP 20129 Incoming Materials Control of Packaging Material
- (b) (4) SOP 211.84.a.6 Incoming Inspections
- (b) (4) SOP 211.100.b.i.7 Creating Requisitions and Purchase Orders in JDE
- (b) (4) SOP C-QA-055, Quality Inspection of Bulk Product
- (b) (4) SOP C-QA-058, Quality Inspection of Printed Components.

Per the firm, the adequacy of specified requirements contained in the purchasing documents is verified prior to their release to the supplier. Purchasing records are maintained and incoming materials are identified and verified per specifications prior to release for use. Records of receiving inspection are maintained.

The Quality Agreements also address the controls on purchasing activities.

The information provided by the firm has adequately addressed the requirements of 21 CFR 820.50.

Corrective and Preventive Action (CAPA), 21 CFR 820.100

The firm stated that the identification and implementation of corrective and preventative actions resulting from investigations of complaints, product rejections, deviations, recalls, audits, regulatory inspections and findings, annual product review, and trends from process performance and product quality monitoring are managed under Biogen Idec procedure GLBL-24504, Corrective Action and Preventative Action (CAPA). Corrective actions are taken to address the cause of nonconformities in order to prevent recurrence. Preventative actions are

identified and implemented to address the causes of potential nonconformities to prevent occurrence.

Records of all such actions are generated and maintained.

Per the firm, deviations received from CMOs are tracked and monitored as outlined in the respective Quality Agreements. Associated CAPAs are tracked and managed through the CMOs Quality Management System. The CAPA reports are provided by each CMO and reviewed by the firm. Per the firm, the CAPA effectiveness is reviewed by both parties as part of the periodic management review meetings.

The information provided by the firm has adequately addressed the requirements of 21 CFR 820.100.

Installation, 21 CFR 820.170

Installation is not required for this combination product.

Servicing, 21 CFR 820.200

Servicing is not required for this combination product.

MANUFACTURING

Biogen Idec states that they utilize (b) (4) as a contract manufacturer for DAC HYP pre-filled syringe (PFS) drug product. Per the firm, the following manufacturing related activities are performed at the (b) (4) facilities;

- Drug Substance Receipt and Storage at the Manufacture Site
- Drug Product Manufacturing
- Component and Equipment Preparation
- (b) (4) Testing
- Quality Control Testing
- Bulk Packaging
- Product Storage



Acceptance Activities

Per the firm, the staked needle syringes are purchased from the vendor (b) (4)

(b) (4) The plunger stopper is a grey (b) (4) The plunger stopper is currently manufactured by (b) (4) using a (b) (4) formulation and complies with the requirements of the current USP <381> and Ph. Eur. 3.2.9. (b) (4) (b) (4) Per the firm, the plunger stoppers meet a sterility assurance level (b) (4) Information provided on acceptance activities is limited to purchase control description.

The firm provided a detail explanation of the controls for the critical steps for the DAC HYP pre-filled syringe (PFS) drug product manufacturing process. Per the firm, the criticality of process steps is determined systematically through a risk analysis of the drug product process. Process inputs and outputs are defined and then assessed based on their potential impact on product quality, process yields, and likelihood of occurrence. The firm provided the (b) (4) controls and tests (b) (4) and the (b) (4) test for visual inspection that are performed (b) (4) The firm also provided the corresponding action limits for the tests and inspections.

According to the firm, finished goods may be shipped (b) (4) During shipments, the temperature of the finished goods is monitored and confirmed to maintain 2–8°C for the entire duration of the transport. The firm provided verification, and validation data for this process.

Per the firm, for smaller volume shipments, finished goods are shipped in insulated shippers from the designated distribution sites. The firm provided verification, and validation data for this process.

Documentation Review Recommendation

The application was searched for documents pertaining to the manufacturing of the combination product. The documentation review of the application for compliance with the applicable Quality system Requirements showed no deficiencies. No additional information is required for the documentation review.

RECOMMENDATION

The application for Daclizumab (PFS) - BLA 761029 is approvable from the perspective of the applicable Quality System Requirements. The documentation review of the application for compliance with the Quality System Requirements showed no deficiencies. The recommended inspection(s) were conducted and deemed acceptable.

Christopher J. Brown -S
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Christopher J Brown, P.E.

Prepared: CJBrown: 03/31/2016
Reviewed: VVerna: 04/04/2016

CTS No.: ICC1500646
BLA 761029

Review Cycle Meeting Attendance:
N/A

To: ORA

Inspectional Guidance

Biogen Idec, Inc.
225 Binney Street,
Cambridge, Massachusetts, 02142-1453, United States,
FEI #: 1220951

[REDACTED] (b) (4)
[REDACTED]
[REDACTED]
FEI # [REDACTED] (b) (4)

CDRH recommends that the next in inspection at the firms listed above covers compliance with all the requirements of 21 CFR part 4, including the applicable Quality System (21CFR 820) requirements – Management Controls (21 CFR 820.20), Design Controls (21 CFR 820.30), Purchasing Controls (21 CFR 820.50), and CAPA (21 CFR 820.100).

REGULATORY STRATEGY

The establishment inspection report (EIR) for the firm should be shared with CDRH (The EIR should be assigned to CDER and then sent to CDRH as a consult for review). If the inspection is being classified Official Action Indicated (OAI), the District should consider recommending appropriate regulatory action with consultation from CDER and CDRH and whether the violation is drug or device related.

Questions regarding this consult should be referred to one of the following individuals:

Primary Contact

Christopher J Brown., P.E.
Mechanical Engineer,
REGO/DMQ/OC/CDRH
Office of Compliance, WO66 RM 3428
Phone: 301-796-0380

Secondary Contacts (if Primary is unavailable and a timely answer is required)

LT Viky Verna,
Combination Product Branch Lead, Senior Regulatory Officer
REGO/DMQ/OC/CDRH
Office of Compliance, WO66 RM 3435
Phone: 301-796- 5770

THIS ATTACHMENT IS NOT TO BE PROVIDED TO THE FIRM OR SHOWN TO THEM DURING THE INSPECTION. THIS ATTACHMENT CONTAINS PREDECISIONAL INFORMATION



DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
Office of New Drugs – ODE IV
Division of Pediatric and Maternal Health
Silver Spring, MD 20993
Telephone 301-796-2200
FAX 301-796-9855

M E M O R A N D U M

From: Donna Snyder, MD,
Acting Pediatric Team Leader
Division of Pediatric and Maternal Health (DPMH)

Through: John Alexander, MD, MPH,
Acting Deputy Director
Division of Pediatric and Maternal Health (DPMH)

To: Division of Neurology Products (DNP)

Drug: Daclizumab (ZINBRYTA) injection for
subcutaneous use, 150 mg/mL single-dose prefilled
syringe

BLA: 761029

Applicant: Biogen Idec

Indication: Treatment of adult patients with relapsing multiple
sclerosis (RMS) who have had an inadequate
response to two other drugs used to treat MS.

Subject: Labeling and Review of Pediatric Review
Committee (PeRC) Paperwork

Materials Reviewed:

- DNP letter to the sponsor confirming agreement with the iPSP, dated December 1, 2014, DARRTS Reference ID: 3664844
- DPMH consult request dated March 3, 2015, DARRTS Reference ID: 3711651
- BLA 761029 Late Cycle Background package, dated February 18, 2016, DARRTS Reference ID: 3889229
- Division Directors Review of BLA 103948, Lemtrada (alemtuzumab) dated November 14, 2014, DARRTS Reference ID; 3658615
- DPMH Review dated October 17, 2014, DARRTS Reference ID: 3642594
- John R. Senior, M.D., Associate Director for Science (Hepatology), Office of Pharmacovigilance and Epidemiology (OPE) review dated January 18, 2016, DARRTS Reference ID: 3874751
- Mark Avigan, MD, CM Review dated November 9, 2015, DARRTS Reference ID: 3844895
- Draft Clinical Review by Lawrence Rodichok, MD, dated June 25, 2015
- Draft Safety Review by Maria Lourdes Villalba, MD, dated February 25, 2016
- Draft labeling submitted by the sponsor and edited by DNP
- PeRC paperwork

Background:

DPMH was consulted to participate in the review a new biologics license application (BLA) for daclizumab [(ZINBRYTA) 150 mg/mL single-dose prefilled syringe for subcutaneous use] submitted for the treatment of adults with relapsing multiple sclerosis (RMS). Daclizumab high yield process (DAC HYP) is a recombinant humanized immunoglobulin G1 (IgG1) monoclonal antibody that binds to the CD50 alpha sub-unit of the human high affinity interleukin-2 receptor (CD-25). A related product, Daclizumab Nutley (Zanapax®, BLA 103749), was approved on December 10, 1997, for prophylaxis of acute organ rejection in adults and pediatric patients 11 month of age and older receiving renal transplants. Daclizumab Nutley also targets CD25 but is not considered to be interchangeable with DAC HYP. Safety data from the use of Daclizumab Nutley will be included as supportive information for the DAC HYP application.

An initial Pediatric Study Plan (PSP) was submitted on February 28, 2014. After discussion with the Division, the sponsor submitted a revised Pediatric Study Plan (PSP) on October 24, 2014. The Division sent an agreed PSP letter to the sponsor on December 1, 2014. The studies agreed to in the iPSP are detailed below:

Pediatric Plan Summary

The applicant requested a partial waiver under the Pediatric Research Equity Act (PREA) for pediatric patients less than 10 years of age on the basis that studies are impractical due to the extremely low prevalence of MS in this specified age group in the pediatric population. The sponsor submitted data on the incidence and prevalence of MS for pediatric patients gathered from literature and from review of claims databases. The prevalence of MS overall, in the US, is estimated to be between 99 and 177/100,000 of

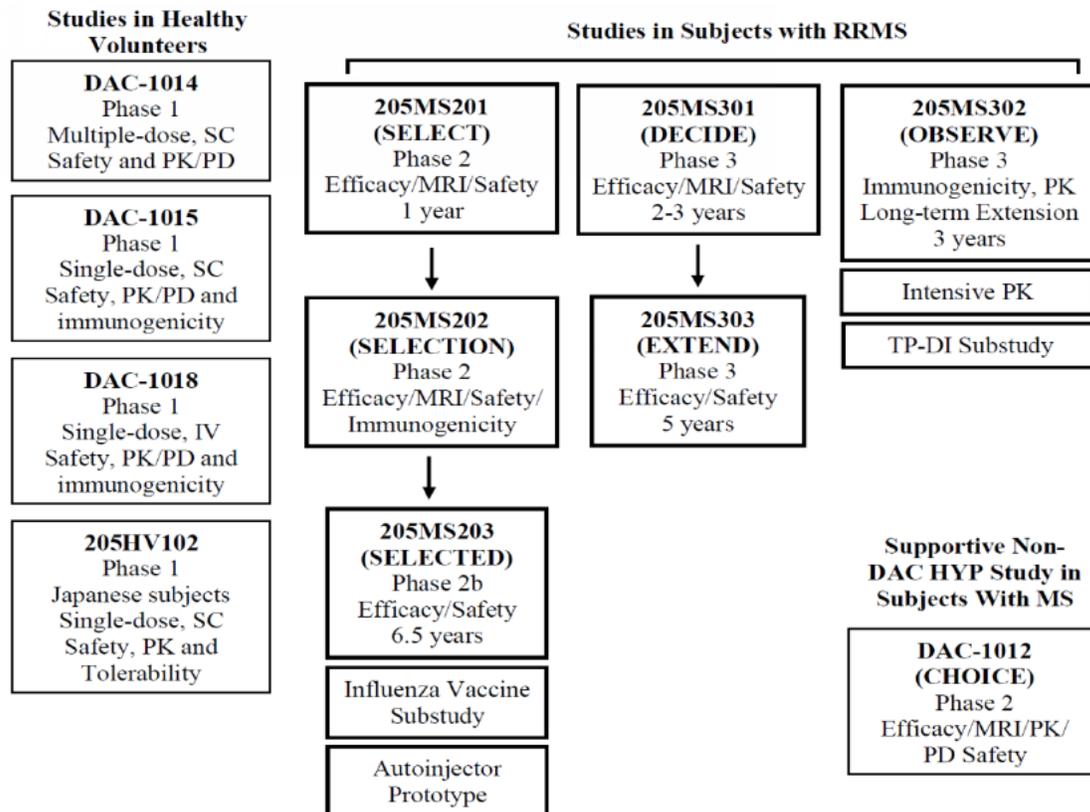
the population, with approximately 300,000 to 500,000 patients affected. A maximum of 3% of patients experience the first MS symptoms before 18 years of age, and 0.07% to 0.12% or 350 to 600 patients experience onset at less than 10 years of age.

The applicant requested a deferral of pediatric studies on the grounds that the pediatric studies had not been completed and the product is ready for approval in adults. (b) (4)

Reviewer comment: The partial waiver and deferral plan submitted by the sponsor is consistent with other recently approved MS products. (b) (4)

Brief Summary of the Submission

The applicant submitted the following studies for review to support the safety and efficacy of the product in adult patients [taken from Dr. Villalba's Safety Review, originally from the applicant's Safety Update Report (SUR)]:



The Division concluded that treatment with Daclizumab (ZINBRYTA) 150 mg subcutaneously (SC) given every 4 weeks is statistically superior to treatment with interferon beta interferon 1a (IFN β 1a, AVONEX) given weekly at a dose of 40 μ g intramuscularly (IM) in reducing the Annualized Relapse Rate (ARR) in patients with RRMS. The product was not shown to provide a benefit in terms of reducing longer term disability when compared to IFN β 1a, but the studies were of not of a long enough duration or large enough to adequately assess this endpoint. Daclizumab did reduce several MRI measures of disease activity, but since these measures are not specifically linked to patient function, the reduction was only supportive of efficacy in the patient population studied.

During the course of the review several safety concerns were identified with a disproportionate number of adverse events in the Daclizumab arm compared to the IFN β 1a arm. These safety concerns included 2 deaths considered to be drug related in the daclizumab arm, liver failure secondary to autoimmune hepatitis (AIH) and infectious complication of dyshidrotic eczema. Non-fatal events included drug-induced liver injury (DILI) in 1% of patients and cutaneous reactions in 20% of patients with at least 3 cases consistent with multi-organ hypersensitivity/drug reaction with eosinophilia and systemic symptoms (DRESS). Additionally, 4% of patients were classified as having autoimmune disorders, including one case of adult Kawasaki disease, one case of sepsis/fever, one case of hemophagocytic syndrome and one case of adult Still's disease. Other events with disproportionate outcomes were infections, seizures, and lymphadenopathy. There were a larger number of breast cancer patients in the safety database than would be expected based on the background rate in the population (185 compared to a 126 per 100,000 population rate), with 9 cases (8 females, 1 male) in daclizumab treated patients and no cases in IFN β 1 treated patients.

The Division has concluded that daclizumab is associated with more serious risks than IFN β 1, but is efficacious and may be of benefit to a select group of MS patients who may have exhausted other treatment options. As a result, daclizumab, if approved, will be indicated for use as a second line therapy and limited to patients who have not responded well to other treatments. The product will likely require a Risk Evaluation and Mitigation Strategy (REMS).

Because of the safety concerns with this product, the Division has determined that a full waiver will be granted for pediatric studies on the grounds that the product would be unsafe in all pediatric age groups.

Reviewer comment: DNP issued a similar waiver for alemtuzumab (LEMTRADA), a CD52 directed cytolytic monoclonal antibody indicated for the treatment of RRMS. Labeling states that "Because of its safety profile, the use of LEMTRADA should generally be reserved for patients who have had an inadequate response to two or more drugs indicated for the treatment of MS" and "Use of LEMTRADA is not recommended in pediatric patients due to the risks of autoimmunity, infusion reactions, and because it may increase the risk of malignancies (thyroid, melanoma, lymphoproliferative disorders, and lymphoma)."

Discussion:

PEDIATRIC USE LABELING

The Pediatric Use subsection must describe what is known and unknown regarding use of the drug in the pediatric population, including limitations of use, and must highlight any differences in efficacy or safety in the pediatric population versus the adult population. For products with pediatric indications, the pediatric information must be placed in the labeling as required by 21 CFR 201.57(c)(9)(iv). This regulation describes the appropriate use statements to include in labeling based on findings of safety and effectiveness in the pediatric use population. This product will not be approved in the pediatric population. As noted above, a waiver will be granted under PREA for the entire pediatric population on the grounds the product would be unsafe in all pediatric age groups. When pediatric studies are waived under PREA because there is evidence that the product would be ineffective or unsafe in pediatric patients, the safety concern must be described in labeling (section 505B(a)(4)(D) and 505B(b)(2)(D) of the FD&C Act (21 U.S.C. 355(c))). DPMH is in agreement with the labeling proposed for section 8.4 by the Division at the meeting on March 1, 2016. See below for the proposed language and the approval letter for the final version of labeling.

8.4 Pediatric Use

Safety and effectiveness of ZINBRYTA in (b) (4) patients (b) (4) years old have not been established. Use of ZINBRYTA is not recommended in pediatric patients due to the risks of hepatic injury, autoimmune and (b) (4) immune-mediated (b) (4) [see *Warnings and Precautions* (5.1, 5.2, 5.3, 5.9)].

DPMH Recommendations and Conclusions

DPMH met with the Division on March 1, 2016 to discuss pediatric labeling. DPMH reviewed the documents required by PeRC in advance of the PeRC meeting. DNP met with the PeRC on March 9, 2016 to discuss the plan for a full waiver based on safety. The PeRC agreed with the Division's plan for a full waiver and reminded the Division that labeling should reflect the safety concern in section 8.4. See the PeRC meeting minutes for a detailed discussion of the issues.

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/s/

DONNA L SNYDER
03/25/2016

JOHN J ALEXANDER
03/28/2016

**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology Review (OSE)
Office of Pharmacovigilance and Epidemiology (OPE)**

Epidemiology: Review of Study on Sarcoidosis among Multiple Sclerosis Patients

Date:	March 10, 2016
Reviewer(s):	Elisa R. Braver, PhD Division of Epidemiology 1
Team Leader	Lockwood Taylor, PhD Division of Epidemiology 1
Division Director	Cunlin Wang, MD, PhD Division of Epidemiology 1
Drug Name(s):	Daclizumab
Subject	Sarcoidosis among Multiple Sclerosis Patients
Application Type/Number:	BLA 761029
Applicant/sponsor:	Biogen
OSE RCM #:	2016-455

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EXECUTIVE SUMMARY

The purpose of this review is to evaluate Biogen's report on the incidence and prevalence of sarcoidosis among multiple sclerosis (MS) patients, which was done in response to a request by FDA to compare sarcoidosis rates observed among MS patients treated with daclizumab (DAC) (N=9) with sarcoidosis rates in the general population of MS patients, almost all of whom have not been treated with DAC.

The study design was a matched-pair cohort in which sarcoidosis incidence and prevalence rates were compared for a cohort of 150,881 MS patients versus 452,094 matched insured-population comparison cohort members without MS (3:1 matching). The sponsor used IMPACT Data Mart, a US health insurance claims database that included 48 health insurers covering 89 million people during the study period of January 1, 2004- December 31, 2014. The sponsor reported an incidence rate ratio of (b) (4) (95% confidence interval: (b) (4)) for sarcoidosis among MS patients compared with matched patients without MS. Based on this result, the sponsor concluded that the sarcoidosis incidence rate among patients treated with DAC during clinical trials was no higher than would be expected among a population of MS patients.

The sponsor's report findings suggest that MS, and not DAC specifically, may be a risk factor for development of sarcoidosis, but the report is inconclusive due to flaws in the methods for analyzing the insurance claims database. The limitations include lack of analyses that accounted for factors that were originally used to match MS patients with comparison patients without MS (i.e., age, birth year), lack of adjustment for race, and differences in duration of follow-up. On average, MS cohort members were followed for 3.35 years versus 1.74 years for the matched control cohort, so that MS cohort members had a longer period of time to be diagnosed with sarcoidosis.

DEPI recommends the following to the sponsor.

- Ensure that analyses of sarcoidosis incidence rates are restricted to newly diagnosed MS patients, matched comparison cohort members, and newly diagnosed sarcoidosis cases by requiring that each eligible cohort member be enrolled in their insurance plan for a minimum of 6 months without having any prior claims of either MS or sarcoidosis.
- Add analyses appropriate for a matched-pair cohort, including analyses to account for differences in follow-up time and time to development of sarcoidosis (e.g., conditional Cox regression, Kaplan-Meier curves, conditional Poisson regression for matched pairs).
- If feasible, include race in the analyses, either via matching or as a covariate because race is associated both with MS and with sarcoidosis.
- Perform sensitivity analyses for a more specific definition of sarcoidosis to include at least two ICD-9 diagnosis codes.
- Explain how the index dates were chosen for the MS and comparison groups in the supplemental report on sarcoidosis. Consider choosing matched comparison group members who had medical visits near the time that MS first was diagnosed in the MS cohort members as one method to ensure that matched comparison patients were at risk during the same time period as when MS patients entered the cohort. Explain how comparison patients who subsequently developed MS were addressed in the data analyses.
- Discuss the strengths and limitations of the IMPACT database used for analyses, including types of plans, average duration of enrollment, and duplication of patients who changed health plans.

1 INTRODUCTION

The purpose of this epidemiology review is to evaluate Biogen's report on the incidence and prevalence of sarcoidosis among multiple sclerosis (MS) patients and the general population. Biogen's report was done in response to a request by FDA to compare sarcoidosis rates observed among MS patients treated with daclizumab (DAC) (N=9) with sarcoidosis rates in the general population of MS patients, almost all of whom have not been treated with DAC.

There are no published epidemiologic studies of the incidence or prevalence of sarcoidosis among MS patients. Some authors have reported cases of sarcoidosis among MS patients treated with interferon-beta (Capobianco 2014; Carbonelli 2012; Chakravarty 2012), but these case reports were unable to distinguish between a drug adverse effect versus other etiologic factors, including the underlying disease.

Sarcoidosis is a disease in which nodules of immune system cells (granulomas) are formed in organs. The affected organs can include the lung, liver, kidney, spleen, heart, brain, eye, skin, and other organs. Sarcoidosis is a diagnosis that is made after ruling out other causes of granulomas. Sarcoidosis can go into remission or not cause clinically significant symptoms; however, about 2,300 people die from sarcoidosis annually in the United States (Swigris 2011). Groups with elevated risk for developing sarcoidosis are females and blacks. Sarcoidosis risk increases with age. Both genetic and environmental factors are thought to contribute to the development of sarcoidosis (Iannuzzi 2007).

2 REVIEW METHODS AND MATERIALS

2.1 DOCUMENT TO BE REVIEWED

- Response to information request on sarcoidosis cases submitted by Biogen dated February 1, 2016

3 REVIEW RESULTS

The objective of the sponsor's in-house epidemiologic report was to compare the incidence rates and prevalence of sarcoidosis among a cohort of 150,881 MS patients versus 452,094 matched insured-population comparison cohort members to determine whether MS was associated with a higher risk of developing sarcoidosis. The study design was a matched-pair cohort.

The data source was a database of US health insurance claims, IMPACT Data Mart, which included 48 health insurers covering 89 million people during the study period of January 1, 2004- December 31, 2014 and about 31 million people per year. The sponsor did not provide further information about the database, including whether the same patients could have been counted more than once during the study period.

MS was defined as having at least two claims listing ICD-9 code 340 and sarcoidosis was defined as having at least one claim listing ICD-9 code 135 following the index date. Each MS cohort member was matched to 3 comparison patients without MS on year of birth, gender, and year of the index date. Index date was not fully explained, but it likely was the date of the MS diagnosis for the MS cohort. The index dates for matched comparison patients were described as being assigned randomly. The average length of follow-up was 3.35 years for the MS cohort and 1.74 years for the matched comparison cohort. The sponsor did not explain how they treated

comparison patients who developed MS after being matched to a patient with MS, including whether these comparison patients were censored or became eligible to switch to the MS cohort. Although the comparison patients were initially matched to the MS patients, the subsequent data analyses did not account for the matched design, so neither age nor gender nor calendar period were controlled for.

The sponsor observed sarcoidosis incidence rates of (b) (4) per 1,000 person-years in the MS cohort and cohort of matched patients, respectively. The incidence rate ratio for sarcoidosis in the MS cohort was (b) (4) (95% confidence interval (CI): (b) (4)) compared with the matched control cohort (Appendix A).

The sponsor noted that the incidence rate of sarcoidosis among patients treated with DAC was (b) (4) per 1,000 person-years of follow-up based on 8 cases among 6,800 person-years of follow-up. The ninth sarcoidosis case was not included in this rate. Incidence rates were not presented for patients in the comparison arms of clinical trials for DAC, but no sarcoidosis cases were reported among comparison patients.

The methods of calculating incidence rates and prevalence were not explained. It appears as though the MS patients were not newly diagnosed. Furthermore, it is unclear whether the sarcoidosis cases were newly diagnosed. Prevalence ratios were consistent with the findings for incidence rates.

Females were 76% of MS patients and 78% of sarcoidosis patients. When stratifying by gender, the incidence rate ratios for sarcoidosis among MS patients were (b) (4) for women (95% CI: (b) (4)) and (b) (4) for men (95% CI: (b) (4)). No analyses were presented by race.

4 DISCUSSION

Crude analyses submitted by the sponsor suggest that sarcoidosis risk is increased among patients with multiple sclerosis compared with the general insured population; however, these analyses are difficult to interpret due to multiple limitations. One major limitation is that the incidence rate calculations are unclear. The sponsor's calculations do not appear to refer to new cases of sarcoidosis occurring among newly diagnosed patients with MS. Generally, a minimum period of enrollment is desirable when using health insurance claims databases to estimate incidence rates so that cohort members cannot have had either prior claims for MS or sarcoidosis during the previous 6 months. One additional major limitation is that MS patients had a longer average follow-up period than the comparison patients; thus MS patients had a longer time at risk of developing sarcoidosis. No analyses accounted for duration of follow-up, including time between cohort entry dates and development of sarcoidosis. A potential limitation is that the definition of sarcoidosis required only one ICD-9 code of 135 although sarcoidosis can be confused with other diseases and is diagnosed by ruling out other diseases causing similar symptoms.

The MS patients participating in the clinical trials of DAC may have been very different than the population of MS patients identified by the sponsor from the IMPACT database, which complicates any comparisons of sarcoidosis incidence rates between DAC-treated patients and MS patients not in the trial. Clinical trial participants usually differ from other patients with the same disease in both demographic and disease characteristics. As a result, the findings from the sponsor's report do not indicate whether the observed sarcoidosis cases among DAC-treated patients were higher than would have been expected.

Although the sponsor initially matched comparison patients by birth year, gender, and index date, the match was not maintained in the statistical analyses. The sponsor analyzed the data without taking matching into consideration. There are standard statistical methods for analyzing matched-pair cohort data (Cummings 2004; Rothman 2008) and ignoring them can lead to biased findings (Sjölander 2013). In the absence of analyses that considered the matching, age was not controlled for although sarcoidosis risk increases with age.

Blacks are at higher risk of developing sarcoidosis and MS than whites, but the sponsor presented no analyses by race. African-American race has consistently been shown to be a risk factor for sarcoidosis (Dumas 2016; Cozier 2011; Langer-Gould 2013; Swigris 2011).

The methods for choosing the index dates for the start of follow-up were unclear. Index dates are important because they determine when follow-up begins and how long it continues. The report did not explain whether the index dates were the date that a diagnosis for MS first appeared in a patient's medical record or the date of the second diagnostic code for MS or some other date. The report mentioned random assignment of index dates for the matched comparison patients, but it is unclear how this was done. A better method for selecting index dates among comparison patients would be choosing dates of visits to a health care provider close to the time that the MS patient first was diagnosed.

The potential for additional study limitations was difficult to assess given how little information was presented about the IMPACT database that was the source for the MS patients, matched comparison patients, and sarcoidosis cases. Information such as patient duplication in health plans, average enrollment duration in health plans, as well as specific types of plans (i.e., HMO, government, etc.) was not provided by the sponsor.

5 CONCLUSION

The sponsor's report findings suggest that MS, independent of DAC, may be a risk factor for development of sarcoidosis, but the report is inconclusive due to flaws in the methods for analyzing the insurance claims database.

6 RECOMMENDATIONS

DEPI recommends the following to the sponsor.

- Ensure that analyses of sarcoidosis incidence rates are restricted to newly diagnosed MS patients, matched comparison cohort members, and newly diagnosed sarcoidosis cases by requiring that each eligible cohort member be enrolled in their insurance plan for a minimum of 6 months without having any prior claims of either MS or sarcoidosis.
- Add analyses appropriate for a matched-pair cohort, including analyses to account for differences in follow-up time and time to development of sarcoidosis (e.g., conditional Cox regression, Kaplan-Meier curves, conditional Poisson regression for matched pairs).
- If feasible, include race in the analyses, either via matching or as a covariate because race is associated both with MS and with sarcoidosis.
- Perform sensitivity analyses for a more specific definition of sarcoidosis to include at least two ICD-9 diagnosis codes.
- Explain how the index dates were chosen for the MS and comparison groups in the supplemental report on sarcoidosis. Consider choosing matched comparison group members

who had medical visits near the time that MS first was diagnosed in the MS cohort members as one method to ensure that matched comparison patients were at risk during the same time period as when MS patients entered the cohort. Explain how comparison patients who subsequently developed MS were addressed in the data analyses.

- Discuss the strengths and limitations of the IMPACT database used for analyses, including types of plans, average duration of enrollment, and duplication of patients who changed health plans.

CC: Zerislassie E/ Calloway P / Braver E / Taylor L / Wang C / OSE

Kelley L / Wheelous T/ Villalba L / Hughes A / Yasuda S / Phipps C / DNP

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8 APPENDICES

8.1 APPENDIX A. SPONSOR'S TABLE OF INCIDENCE RATES, INCIDENCE RATE RATIOS, AND 95% CONFIDENCE INTERVALS

Table 2: Incidence Rate of Sarcoidosis in MS cases (N = 150,881) and matched general population (GP) controls (N = 452,094) in IMPACT database (2004-2014)

	Number of sarcoidosis cases	Person-yrs of observation	Incidence rate per 1,000 person-yr (95% CI)	Incidence rate ratio	95% CI
All cases	(b) (4)	(b) (4)			(b) (4)
MS cohort					
Matched GP cohort					
Women					
MS cohort					
Matched GP cohort					
Men					
MS cohort					
Matched GP cohort					

GP = general population; MS = multiple sclerosis

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/s/

ELISA R BRAVER
03/10/2016

LOCKWOOD G TAYLOR
03/10/2016

CUNLIN WANG
03/11/2016

3-4-16

To: Dr. Lourdes Villaba, ODE1, OND and Drs. Mark Avigan and John Senior, OSE, OPE

From: Amy Rosenberg, MD, OBP, OPQ

Amy S. Rosenberg

-A

Digitally signed by Amy S. Rosenberg -A
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA,
ou=People, ou=2342.19200300.100.1.1=1300045963,
cn=Amy S. Rosenberg -A
Date: 2016.03.15 11:47:50 -0400

Through: Daniela Verthelyi, Ph.D., M.D, OBP, OPQ

Re: Consult on Autoimmune AEs in the context of treatment of MS patients with Daclizumab (anti-IL-2Ra mAb).

I was asked to consult on adverse events stemming from the use of Daclizumab Hyp in the setting of treatment for relapsing-remitting Multiple Sclerosis. This agent, a CD25 (IL-2R α) mAb targets the alpha chain of the high affinity IL-2 receptor which is expressed transiently on activated T effector cells, but critically, is expressed constitutively at high levels on regulatory T cells (Treg). Tregs arise from two sources: natural Tregs which originate in the thymus and are specific for autoantigens in the context of self HLA; and peripheral Tregs which arise in the periphery under immune suppressive conditions. These cells potently suppress autoimmune effector T cells, as their deletion, or blockade of their function in the following settings leads to severe autoimmune disease:

- 1) Rare patients with mutations in the IL-2Ra gene who manifest the following: increased susceptibility to infection; lymphoproliferation, extensive lymphocytic infiltration of tissues including lung, liver, intestine and bone and inflammation (Sharfe N et al Humjan immune disorder arising from mutation of the alpha chain of the interleukin 2 receptor. PNAS 1997); primary biliary cirrhosis (PBC) in a 5 year old patient with loss of IL-2RA, with intense lymphoid infiltration of the portal tracts, the typical serologic profile of PBC patients (anti-mitochondrial antibodies) who achieved a full cure only by allogeneic stem cell transplant (Aoki C et al IL-2Ra deficiency and features of primary biliary cirrhosis. J. Autoimmunity 2006); an IPEX like syndrome consisting of endocrinopathies, eczema, hemolytic anemia, lymphadenopathy, hepatosplenomegaly and enteropathy (Caudy A et al CD25 deficiency causes an immune dysregulation, polyendocrinopathy, enteropathy, X-linked like syndrome and defective IL-10 expression from CD4 lymphocytes J. Allergy and Clinical Immunology 2007); progressive manifestations of autoimmunity including enteropathy, skin disease (pemphigoid) with aggressive infiltration of CD8+ T cells, endocrinopathy, as well as immune deficiency to infectious agents (Goudy K et al Human IL2RA null mutation mediates immunodeficiency with lymphoproliferation and autoimmunity. Clin Immunol. 2013). These reports are attached
- 2) Patients with mutations in the FOXP3 transcription factor essential for Treg development/stability who develop the IPEX syndrome, consisting of Immune

dysregulation, polyendocrinopathy, enteropathy, X linked (Bacchetta R et al. From IPEX syndrome to *FOXP3* mutation: a lesson on immune dysregulation. Ann. NYAS 2016) ;

- 3) Patients with mutations in the CTLA-4 molecule, critical for regulatory T cell function who manifest lymphoproliferation and lymphocytic infiltration in multiple organs, autoimmune cytopenias and B cell abnormalities (Kuehn, H.S., *Ouyang, W.*, Lo, B., Deenick, E.K., Niemela, J.E., Avery, D.T., Schickel, J.-N., Tran, D.Q., Stoddard, J., Zhang, Y., *Frucht, DM* et al. (2014). Science 345, 1623–1627. (OBP contributors in italics)
- 4) Tumor immunotherapy wherein the deliberate deletion or blockade of Tregs via mAbs directed to CTLA4 (expressed highly on Tregs, ipilimumab) or PD-1, a checkpoint inhibitor, not only is associated with anti-tumor responses, but also with profound autoimmunity (see below and product label for Yervoy; Tarhini A Immune mediated adverse events associated with CTLA-4 blockade therapy: the underlying mechanisms and clinical management. Scientifica 2013);
- 5) Mouse models in which CD25R α (or IL-2) is genetically deleted with the consequent development of severe lymphoproliferation and other manifestations of autoimmunity including hemolytic anemia (Willerford D et al Interleukin-2 Receptor α Chain Regulates the Size and Content of the Peripheral Lymphoid Compartment Immunity 1995 and Sadlack B Generalized autoimmune disease in interleukin 2 deficient mice is triggered by an uncontrolled activation and proliferation of CD4+ T cells Eur.J. Immunol. 1995).

Although DAC had previously been approved for prevention of allograft rejection and autoimmune phenomena were not described in that clinical context, it must be remembered that the agent was given as a short course to patients concomitantly with several other immune suppressive agents whereas in these studies, DAC was administered chronically over a prolonged time frame in the absence of potent immune suppressive agents such as cyclosporinA or tacrolimus.

In the development of DAC for MS, an autoimmune condition, there was a robust safety data base from which safety signals arose that pertained specifically or more commonly to patients treated with DAC and not with control IFN- β or placebo treatment. AEs, some severe, were observed including hepatitis, colitis, skin rashes (both psoriaform and eczematous), severe MS relapse/progression, lymphadenopathy, lymphoma, thrombocytopenia and hemolytic anemia and infection. In fact, the 5 deaths observed in DAC treated patients in these studies pertained to autoimmune mediated hepatitis, cutaneous drug reactions, as well as worsened MS (2-3 months after the last treatment of DAC, considered within the treatment period) likely attributable to more severe autoimmunity. In the one patient on study in which death was attributed to a fall, she had precedent diarrhea and weakness, a well-known manifestation of colitis, as well as lymphadenopathy/lymphoproliferation. SAEs more common in DAC treated patients include

serious infection, hematologic (including hemolytic anemia, thrombocytopenia and lymphadenopathy) skin, GI and liver related events. Importantly, there was no evidence of a dose response as one might expect with traditional drug toxicities. These findings and their similarity to the autoimmune responses induced by ipilimumab, natural mutations in CD25R α and CTLA-4 in humans, and KO of these receptors in mice coupled with the documentation of DAC's depletion of Tregs (*vide infra*) in patients implicates autoimmunity as the pathogenesis of these AEs.

The sponsor submitted study data demonstrating that FOXP3+ regulatory T-cells were diminished by 60% within 8 weeks in study subjects treated with DAC HYP with the levels of such cells then remaining stable during DAC HYP treatment for up to 3 years. The reduction in numbers of these FOXP3+ T-cells is not surprising as regulatory T cells express high levels of CD25, the target antigen of this IgG1 mAb which has been shown to have ADCC activity. Whether, as the sponsor contends, these remaining Tregs were functionally competent based on maintenance of "markers associated with Treg lineage stability and phenotype" (Summary of Clinical Pharmacology Studies; 2.7.2) is not clear given the full saturation of CD25R α in treated patients, thus blocking the ability of Tregs to respond to IL-2 and thereby exert suppressive function. After discontinuation of the anti-CD25 monoclonal treatment in MS patient study subjects, recovery of the FOXP3+ regulatory T-cell population is gradual and only returned to baseline approximately 20-24 weeks (5-6 months) after the last dose of DAC HYP. Thus, the development of autoimmune disease for a substantial time after discontinuation of the drug does not diminish causality of DAC in these events.

Dr. Avigan's excellent evaluation of the autoimmune hepatitis incidents is as follows. There has been a consistent imbalance in the percentages of treatment-associated liver injury cases in study subjects randomized to receive the monoclonal antibody vs placebo or an active comparator (IFN-b-1a). At least 7 cases of clinically significant liver injury were marked by autoimmune features raising a concern that a potential unintended consequence of treatment with DAC HYP in some patients is induction of autoimmune liver injury by anti-CD25 inhibition of regulatory T cell suppression. DAC HYP –induced autoimmune organ injury is further supported by an adverse event profile that also includes cases of treatment-associated colitis and a range of skin reactions.

From Dr. Villaba's excellent summary there was also an imbalance in SAEs pertaining to GI disorders with one case of Crohn's, one case of UC, one of colitis, and one of enterocolitis in DAC treated patients. Moreover there were an excess of SAEs pertaining to skin disorders including dermatitis, psoriasis, angioedema, DRESS, and leukocytoclastic vasculitis in DAC treated patients (*vide infra*). Further evaluation of other autoimmune manifestations from her review is as follows:

Cutaneous reactions: Cutaneous reactions occurred in 894 of 2236 DAC-treated subjects (40% of all exposed patients), *of which 13% were serious, severe or led to drug withdrawal (5% of all*

patients exposed to DAC HYP). 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 therapeutic approach and action with respect to DAC HYP. There were at least 3 cases consistent with multiorgan hypersensitivity/drug reaction with eosinophilia and systemic symptoms (DRESS). Some patients required hospitalization, administration of topical tacrolimus or systemic corticosteroids, or plasmapheresis. Time to resolution in some cases required months and in some cases whether the reaction resolved or not was unknown as of September 2015.

Colitis

There was an imbalance of colitis-related AEs on DAC 150 (14 cases) vs none in the IFN β 1a arm in Study 301. Some immune mediated reactions required hospitalizations, invasive procedures such as duodenoscopy, sigmoidoscopy, and colonoscopy for such AEs. Furthermore, and as excellently expressed, the sponsors failed to capture several events associated with autoimmunity and thus underestimated the risk of autoimmune disease associated with DAC as indicated below:

Immune mediated/autoimmune/systemic inflammatory syndrome: In addition to AIH and autoimmune skin reactions such as psoriasis, autoimmune diseases in ≥ 2 subjects included the following: Sarcoidosis n=9 (0.4%) (five of which were reported after the cutoff of the SUR) , Celiac disease n=4, Interstitial lung disease n=5, Vitiligo n=3, Hemolytic anemia n=2, Thrombocytopenia n=4, Type 1 diabetes mellitus =2, Glomerulonephritis n=2, RA =2. Importantly, some patients presented concurrent or sequential immune related conditions including the following:

- a) systemic inflammatory syndrome with multiorgan failure with unknown source (sepsis vs. immune mediated) in at least 4 patients (including one hemophagocytic syndrome and one Kawasaki's disease). Patients were treated with antibiotics and high dose corticosteroids and/or plasmapheresis. This syndrome overlaps with DRESS. If considered altogether, there are 7 cases of multiorgan hypersensitivity.
- b) lymphadenopathy: n=137 (6% of all exposed). Of those, 25% were serious, severe or led to drug withdrawal. Most such cases were not well characterized including several cases highly suggestive of sarcoidosis but lacking a definitive workup.

From an immunologic standpoint, these findings indicate that in a substantial number of patients, treatment with DAC eliminated CD25 expressing Tregs and that this deficit was not compensated by potential other immunologic control mechanisms (eg CD56 hi NK cells) and resulted in serious autoimmune disease. In fact, this spectrum of SAEs is strikingly similar to those of ipilimumab treated cancer patients (see below), and similar to patients heterozygous for mutations in CD25Ra and CTLA4. Ipilimumab is a mAb that depletes and/or blocks the function

of Tregs which express high levels of CTLA4 (as they also do of CD25). This agent is approved in immunotherapy of cancer and has a high rate of AEs pertaining to autoimmunity per below black box warning in the label.

WARNING: IMMUNE-MEDIATED ADVERSE REACTIONS

YERVOY can result in severe and fatal immune-mediated adverse reactions due to T-cell activation and proliferation. These immune-mediated reactions may involve any organ system; however, the most common severe immune-mediated adverse reactions are enterocolitis, hepatitis, dermatitis (including toxic epidermal necrolysis), neuropathy, and endocrinopathy. The majority of these immune-mediated reactions initially manifested during treatment; however, a minority occurred weeks to months after discontinuation of YERVOY.

Permanently discontinue YERVOY and initiate systemic high-dose corticosteroid therapy for severe immune-mediated reactions. [See Dosage and Administration (2.2).]

Assess patients for signs and symptoms of enterocolitis, dermatitis, neuropathy, and endocrinopathy and evaluate clinical chemistries including liver function tests and thyroid function tests at baseline and before each dose. [See Warnings and Precautions

-----ADVERSE REACTIONS-----

Most common adverse reactions ($\geq 5\%$) are fatigue, diarrhea, pruritus, rash, and colitis. (6.1)

Patients heterozygous for CTLA4 mutations demonstrated a range of autoimmune disease with onset at a wide range of ages (2-40 years): gut inflammation, cytopenias, pulmonary infiltrates, focal brain inflammation, and hypogammaglobulinemia together with presence of autoantibodies and hyperproliferative lymphocytes (See attached references).

Moreover, these findings are also strikingly similar to both CTLA4 knock out (KO) mice, as well as CD25 KO mice (see attached references).

Additional AEs that pertain to the loss of Tregs and require further evaluation include 1) lymphadenopathy, 2) lymphoma, 3) worsened MS and 4) infections. Indeed, loss of Tregs would be expected to cause substantial lymphoproliferation and perhaps development of lymphoma as a consequence. In the CD25Ra/IL-2 KO mice, although there was robust lymphoproliferation, lymphoma did not develop but this is likely because such mice did not live long enough, with many dying of hemolytic anemia. There were several cases of hemolytic anemia and thrombocytopenia that developed in DAC treated patients. Lastly, many of the patients who died, did so due to infection following particularly severe episodes of MS (brain

stem involvement) in which mucosal barriers were violated (eg aspiration pneumonia). As with other manifestations of autoimmunity, loss of Treg function would be expected to exacerbate MS and thus it is likely that these patients experienced more severe MS due to such loss. The higher incidence of infections was also well noted in patients with mutations in CD25Ra and is likely attributed to blockade of T effector cell function as activated T effector cells also express CD25Ra. In fact, the efficacy of DAC in diminishing MS exacerbations likely pertains to elimination or blockade of such effector cells.

One further unexplored area is the effect of anti drug antibody (ADA) not only on efficacy, but on these safety issues as well. From Dr. Sun's report, is the following:

Treatment-emergent ADAs to DAC HYP 150 mg were observed in 4% and 19% of subjects in Study 201 and Study 301, respectively, while NABs were observed in 3% and 8% of subjects in Study 201 and Study 301, respectively.

- Majority occurred early and decreased with continuous treatment, with majority being transient responses.
- Population PK analysis showed that time-varying NAb-positive status increased the DAC HYP clearance by an average of 19%.

So the question is whether the development of NAB or ADA responses was associated with autoimmunity related AEs. The prediction is that the patients with diminished activity of DAC due to ADA would experience less depletion of Tregs, no or less frequent autoimmunity associated AEs, and perhaps no change in the course/nature of their MS. However, antibodies to DAC may be more likely to be generated in patients with an inflammatory milieu due to autoimmunity. For example, it is intriguing that one of the patients who developed both autoimmune skin disease and autoimmune hepatitis had NABs to DAC documented at day 169, the time at which hepatitis was documented. It is likely that the hepatitis began much earlier (by the time of diagnosis of AIH by liver enzyme assessment, significant tissue damage had already occurred) and antibody mediated neutralization of DAC followed, a manifestation of autoimmunity. Yet, once autoimmune responses were generated, given the extensive amount of time before recovery of Tregs (whether functional or not) following cessation of DAC, the NAB to DAC were of no importance except as further evidence of robust immune responses.

In summary, given the preponderance of evidence, there is no question that there is a significant incidence of SAEs and AEs pertaining to autoimmune disease unleashed by DAC depletion/blockade of Tregulatory function that in such cases was not compensated for by other mechanisms.

Finally, the question is whether such autoimmune related SAEs can be 1) predicted and 2) detected early and 3) successfully mitigated, keeping in mind that Tregs only return to baseline levels over the course of 5-6 months and their function at the time of recovery unknown.

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.
- 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.

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.

Recommendation:

- 1) 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
- 2) I strongly recommend a Center Director Briefing.

**REGULATORY PROJECT MANAGER
PHYSICIAN LABELING RULE (PLR) FORMAT REVIEW
OF THE PRESCRIBING INFORMATION**

Complete for all new NDAs, BLAs, Efficacy Supplements, and PLR Conversion Labeling Supplements

Application: BLA 761029

Application Type: New BLA

Drug Name(s)/Dosage Form(s): Zinbryta (daclizumab), injection

Applicant: Biogen

Receipt Date: February 27, 2015

Goal Date: May 27, 2016

1. Regulatory History and Applicant's Main Proposals

EOP2 Meeting: July 24, 2008

Pre-BLA Meeting: October 8, 2014

Daclizumab-High Yield Process (DAC-HYP; ZINBRYTA™) is a humanized monoclonal IgG1 antibody developed for the treatment of relapsing forms of multiple sclerosis.

2. Review of the Prescribing Information

This review is based on the applicant's submitted Word format of the prescribing information (PI). The applicant's proposed PI was reviewed in accordance with the labeling format requirements listed in the "Selected Requirements of Prescribing Information (SRPI)" checklist (see Section 4 of this review).

3. Conclusions/Recommendations

No SRPI format deficiencies were identified in the review of this PI.

4. Selected Requirements of Prescribing Information

The Selected Requirement of Prescribing Information (SRPI) is a 41-item, drop-down checklist of important format elements of the prescribing information (PI) based on labeling regulations (21 CFR 201.56 and 201.57) and guidances.

Highlights

See Appendix for a sample tool illustrating Highlights format.

HIGHLIGHTS GENERAL FORMAT

Selected Requirements of Prescribing Information

- YES** 1. Highlights (HL) must be in a minimum of 8-point font and should be in two-column format, with ½ inch margins on all sides and between columns.

Comment:

- YES** 2. The length of HL must be one-half page or less unless a waiver has been granted in a previous submission. The HL Boxed Warning does not count against the one-half page requirement. Instructions to complete this item: If the length of the HL is one-half page or less, select “YES” in the drop-down menu because this item meets the requirement. However, if HL is longer than one-half page, select “NO” unless a waiver has been granted.

Comment:

- YES** 3. A horizontal line must separate:
- HL from the Table of Contents (TOC), **and**
 - TOC from the Full Prescribing Information (FPI).

Comment:

- YES** 4. All headings in HL (from Recent Major Changes to Use in Specific Populations) must be **bolded** and presented in the center of a horizontal line. (Each horizontal line should extend over the entire width of the column.) The HL headings (from Recent Major Changes to Use in Specific Populations) should be in UPPER CASE letters. See Appendix for HL format.

Comment:

- YES** 5. White space should be present before each major heading in HL. There must be no white space between the HL Heading and HL Limitation Statement. There must be no white space between the product title and Initial U.S. Approval. See Appendix for HL format.

Comment:

- YES** 6. Each summarized statement or topic in HL must reference the section(s) or subsection(s) of the Full Prescribing Information (FPI) that contain more detailed information. The preferred format is the numerical identifier in parenthesis [e.g., (1.1)] at the end of each summarized statement or topic.

Comment:

- YES** 7. Headings in HL must be presented in the following order:

Heading	Required/Optional
• Highlights Heading	Required
• Highlights Limitation Statement	Required
• Product Title	Required
• Initial U.S. Approval	Required
• Boxed Warning	Required if a BOXED WARNING is in the FPI
• Recent Major Changes	Required for only certain changes to PI*
• Indications and Usage	Required
• Dosage and Administration	Required
• Dosage Forms and Strengths	Required
• Contraindications	Required (if no contraindications must state “None.”)
• Warnings and Precautions	Not required by regulation, but should be present
• Adverse Reactions	Required
• Drug Interactions	Optional
• Use in Specific Populations	Optional
• Patient Counseling Information Statement	Required
• Revision Date	Required

Selected Requirements of Prescribing Information

* RMC only applies to five labeling sections in the FPI: BOXED WARNING, INDICATIONS AND USAGE, DOSAGE AND ADMINISTRATION, CONTRAINDICATIONS, and WARNINGS AND PRECAUTIONS.

Comment:

HIGHLIGHTS DETAILS

Highlights Heading

- YES** 8. At the beginning of HL, the following heading, “**HIGHLIGHTS OF PRESCRIBING INFORMATION**” must be **bolded** and should appear in all UPPER CASE letters.

Comment:

Highlights Limitation Statement

- YES** 9. The **bolded** HL Limitation Statement must include the following verbatim statement: “**These highlights do not include all the information needed to use (insert NAME OF DRUG PRODUCT) safely and effectively. See full prescribing information for (insert NAME OF DRUG PRODUCT).**” The name of drug product should appear in UPPER CASE letters.

Comment:

Product Title in Highlights

- YES** 10. Product title must be **bolded**.

Comment:

Initial U.S. Approval in Highlights

- YES** 11. Initial U.S. Approval must be **bolded**, and include the verbatim statement “**Initial U.S. Approval:**” followed by the **4-digit year**.

Comment:

Boxed Warning (BW) in Highlights

- N/A** 12. All text in the BW must be **bolded**.

Comment:

- N/A** 13. The BW must have a title in UPPER CASE, following the word “**WARNING**” and other words to identify the subject of the warning. Even if there is more than one warning, the term “**WARNING**” and not “**WARNINGS**” should be used. For example: “**WARNING: SERIOUS INFECTIONS and ACUTE HEPATIC FAILURE**”. If there is more than one warning in the BW title, the word “and” in lower case can separate the warnings. The BW title should be centered.

Comment:

- N/A** 14. The BW must always have the verbatim statement “*See full prescribing information for complete boxed warning.*” This statement must be placed immediately beneath the BW title, and should be centered and appear in *italics*.

Comment:

- N/A** 15. The BW must be limited in length to 20 lines. (This includes white space but does not include the BW title and the statement “*See full prescribing information for complete boxed warning.*”)

Selected Requirements of Prescribing Information

Comment:

Recent Major Changes (RMC) in Highlights

- N/A** 16. RMC pertains to only five sections of the FPI: BOXED WARNING, INDICATIONS AND USAGE, DOSAGE AND ADMINISTRATION, CONTRAINDICATIONS, and WARNINGS AND PRECAUTIONS. Labeling sections for RMC must be listed in the same order in HL as they appear in the FPI.

Comment:

- N/A** 17. The RMC must include the section heading(s) and, if appropriate, subsection heading(s) affected by the recent major change, together with each section's identifying number and date (month/year format) on which the change was incorporated in the PI (supplement approval date). For example, "Warnings and Precautions, Acute Liver Failure (5.1) --- 8/2015."

Comment:

- N/A** 18. A changed section must be listed under the RMC heading for at least one year after the date of the labeling change and must be removed at the first printing subsequent to the one year period. (No listing should be one year older than the revision date.)

Comment:

Dosage Forms and Strengths in Highlights

- N/A** 19. For a product that has more than one dosage form (e.g., capsules, tablets, injection), bulleted headings should be used.

Comment:

Contraindications in Highlights

- YES** 20. All contraindications listed in the FPI must also be listed in HL. If there is more than one contraindication, each contraindication should be bulleted. If no contraindications are known, must include the word "None."

Comment:

Adverse Reactions in Highlights

- YES** 21. For drug products other than vaccines, the verbatim **bolded** statement must be present: "**To report SUSPECTED ADVERSE REACTIONS, contact (insert name of manufacturer) at (insert manufacturer's U.S. phone number which should be a toll-free number) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.**"

Comment:

Patient Counseling Information Statement in Highlights

- YES** 22. The Patient Counseling Information statement must include one of the following three **bolded** verbatim statements that is most applicable:

If a product **does not** have FDA-approved patient labeling:

Selected Requirements of Prescribing Information

- See 17 for PATIENT COUNSELING INFORMATION

If a product has (or will have) FDA-approved patient labeling:

- See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling
- See 17 for PATIENT COUNSELING INFORMATION and Medication Guide

Comment:

Revision Date in Highlights

- N/A** 23. The revision date must be at the end of HL, and should be **bolded** and right justified (e.g., “**Revised: 8/2015**”).

Comment:

Selected Requirements of Prescribing Information

Contents: Table of Contents (TOC)

See Appendix for a sample tool illustrating Table of Contents format.

- YES** 24. The TOC should be in a two-column format.
Comment:
- YES** 25. The following heading must appear at the beginning of the TOC: “**FULL PRESCRIBING INFORMATION: CONTENTS.**” This heading should be in all UPPER CASE letters and **bolded**.
Comment:
- N/A** 26. The same title for the BW that appears in HL and the FPI must also appear at the beginning of the TOC in UPPER CASE letters and **bolded**.
Comment:
- YES** 27. In the TOC, all section headings must be **bolded** and should be in UPPER CASE.
Comment:
- YES** 28. In the TOC, all subsection headings must be indented and not bolded. The headings should be in title case [first letter of all words are capitalized except first letter of prepositions (for, of, to) and articles (a, an, the), or conjunctions (or, and)].
Comment:
- YES** 29. The section and subsection headings in the TOC must match the section and subsection headings in the FPI.
Comment:
- YES** 30. If a section or subsection required by regulation [21 CFR 201.56(d)(1)] is omitted from the FPI, the numbering in the TOC must not change. The heading “**FULL PRESCRIBING INFORMATION: CONTENTS***” must be followed by an asterisk and the following statement must appear at the end of the TOC: “*Sections or subsections omitted from the full prescribing information are not listed.”
Comment:

Selected Requirements of Prescribing Information

Full Prescribing Information (FPI)

FULL PRESCRIBING INFORMATION: GENERAL FORMAT

- YES** 31. The **bolded** section and subsection headings in the FPI must be named and numbered in accordance with 21 CFR 201.56(d)(1) as noted below. (Section and subsection headings should be in UPPER CASE and title case, respectively.) If a section/subsection required by regulation is omitted, the numbering must not change. Additional subsection headings (i.e., those not named by regulation) must also be **bolded** and numbered.

BOXED WARNING
1 INDICATIONS AND USAGE
2 DOSAGE AND ADMINISTRATION
3 DOSAGE FORMS AND STRENGTHS
4 CONTRAINDICATIONS
5 WARNINGS AND PRECAUTIONS
6 ADVERSE REACTIONS
7 DRUG INTERACTIONS
8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
8.2 Lactation (if not required to be in Pregnancy and Lactation Labeling Rule (PLLR) format, use "Labor and Delivery")
8.3 Females and Males of Reproductive Potential (if not required to be in PLLR format, use "Nursing Mothers")
8.4 Pediatric Use
8.5 Geriatric Use
9 DRUG ABUSE AND DEPENDENCE
9.1 Controlled Substance
9.2 Abuse
9.3 Dependence
10 OVERDOSAGE
11 DESCRIPTION
12 CLINICAL PHARMACOLOGY
12.1 Mechanism of Action
12.2 Pharmacodynamics
12.3 Pharmacokinetics
12.4 Microbiology (by guidance)
12.5 Pharmacogenomics (by guidance)
13 NONCLINICAL TOXICOLOGY
13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
13.2 Animal Toxicology and/or Pharmacology
14 CLINICAL STUDIES
15 REFERENCES
16 HOW SUPPLIED/STORAGE AND HANDLING
17 PATIENT COUNSELING INFORMATION

Comment:

- YES** 32. The preferred presentation for cross-references in the FPI is the section (not subsection) heading followed by the numerical identifier. The entire cross-reference should be in *italics* and enclosed within brackets. For example, “[see *Warnings and Precautions (5.2)*].”

Comment:

Selected Requirements of Prescribing Information

- N/A** 33. For each RMC listed in HL, the corresponding new or modified text in the FPI must be marked with a vertical line on the left edge.

Comment:

FULL PRESCRIBING INFORMATION DETAILS

FPI Heading

- NO** 34. The following heading “**FULL PRESCRIBING INFORMATION**” must be **bolded**, must appear at the beginning of the FPI, and should be in UPPER CASE.

Comment:

BOXED WARNING Section in the FPI

- N/A** 35. All text in the BW should be **bolded**.

Comment:

- N/A** 36. The BW must have a title in UPPER CASE, following the word “**WARNING**” and other words to identify the subject of the warning. (Even if there is more than one warning, the term, “**WARNING**” and not “**WARNINGS**” should be used.) For example: “**WARNING: SERIOUS INFECTIONS and ACUTE HEPATIC FAILURE**”. If there is more than one warning in the BW title, the word “and” in lower case can separate the warnings.

Comment:

CONTRAINDICATIONS Section in the FPI

- N/A** 37. If no Contraindications are known, this section must state “None.”

Comment:

ADVERSE REACTIONS Section in the FPI

- YES** 38. When clinical trials adverse reactions data are included (typically in the “Clinical Trials Experience” subsection), the following verbatim statement (or appropriate modification) should precede the presentation of adverse reactions from clinical trials:

“Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.”

Comment:

- N/A** 39. When postmarketing adverse reaction data are included (typically in the “Postmarketing Experience” subsection), the following verbatim statement (or appropriate modification) should precede the presentation of adverse reactions:

“The following adverse reactions have been identified during post-approval use of (insert drug name). Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.”

Comment:

Selected Requirements of Prescribing Information

PATIENT COUNSELING INFORMATION Section in the FPI

YES 40. Must reference any FDA-approved patient labeling in Section 17 (PATIENT COUNSELING INFORMATION). The reference statement should appear at the beginning of Section 17 and include the type(s) of FDA-approved patient labeling (e.g., Patient Information, Instructions for Use, or Medication Guide). Recommended language for the reference statement should include one of the following five verbatim statements that is most applicable:

- Advise the patient to read the FDA-approved patient labeling (Patient Information).
- Advise the patient to read the FDA-approved patient labeling (Instructions for Use).
- Advise the patient to read the FDA-approved patient labeling (Patient Information and Instructions for Use).
- Advise the patient to read the FDA-approved patient labeling (Medication Guide).
- Advise the patient to read the FDA-approved patient labeling (Medication Guide and Instructions for Use).

Comment:

YES 41. FDA-approved patient labeling (e.g., Patient Information, Instructions for Use, or Medication Guide) must not be included as a subsection under Section 17 (PATIENT COUNSELING INFORMATION). All FDA-approved patient labeling must appear at the end of the PI upon approval.

Comment:

Selected Requirements of Prescribing Information

Appendix: Highlights and Table of Contents Format

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use **PROPRIETARY NAME** safely and effectively. See full prescribing information for **PROPRIETARY NAME**.

PROPRIETARY NAME (non-proprietary name) dosage form, route of administration, controlled substance symbol
Initial U.S. Approval: YYYY

WARNING: TITLE OF WARNING

See full prescribing information for complete boxed warning.

- Text (4)
- Text (5.x)

RECENT MAJOR CHANGES

Section Title, Subsection Title (x.x) M/201Y
Section Title, Subsection Title (x.x) M/201Y

INDICATIONS AND USAGE

PROPRIETARY NAME is a (insert FDA established pharmacologic class text phrase) indicated for ... (1)

Limitations of Use: Text (1)

DOSAGE AND ADMINISTRATION

- Text (2.x)
- Text (2.x)

DOSAGE FORMS AND STRENGTHS

Dosage form(s): strength(s) (3)

CONTRAINDICATIONS

- Text (4)
- Text (4)

WARNINGS AND PRECAUTIONS

- Text (5.x)
- Text (5.x)

ADVERSE REACTIONS

Most common adverse reactions (incidence > x%) are text (6.x)

To report **SUSPECTED ADVERSE REACTIONS**, contact name of manufacturer at toll-free phone # or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

- Text (7.x)
- Text (7.x)

USE IN SPECIFIC POPULATIONS

- Text (8.x)
- Text (8.x)

See 17 for **PATIENT COUNSELING INFORMATION** and FDA-approved patient labeling **OR** and Medication Guide.

Revised: M/201Y

FULL PRESCRIBING INFORMATION: CONTENTS*

WARNING: TITLE OF WARNING

1 INDICATIONS AND USAGE

2 DOSAGE AND ADMINISTRATION

2.1 Subsection Title

2.2 Subsection Title

3 DOSAGE FORMS AND STRENGTHS

4 CONTRAINDICATIONS

5 WARNINGS AND PRECAUTIONS

5.1 Subsection Title

5.2 Subsection Title

6 ADVERSE REACTIONS

6.1 Clinical Trials Experience

6.2 Immunogenicity

6.2 or 6.3 Postmarketing Experience

7 DRUG INTERACTIONS

7.1 Subsection Title

7.2 Subsection Title

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

8.2 Lactation (if not required to be in PLLR format use Labor and Delivery)

8.3 Females and Males of Reproductive Potential (if not required to be in PLLR format use Nursing Mothers)

8.4 Pediatric Use

8.5 Geriatric Use

8.6 Subpopulation X

9 DRUG ABUSE AND DEPENDENCE

9.1 Controlled Substance

9.2 Abuse

9.3 Dependence

10 OVERDOSAGE

11 DESCRIPTION

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

12.2 Pharmacodynamics

12.3 Pharmacokinetics

12.4 Microbiology

12.5 Pharmacogenomics

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

13.2 Animal Toxicology and/or Pharmacology

14 CLINICAL STUDIES

14.1 Subsection Title

14.2 Subsection Title

15 REFERENCES

16 HOW SUPPLIED/STORAGE AND HANDLING

17 PATIENT COUNSELING INFORMATION

* Sections or subsections omitted from the full prescribing information are not listed.

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

/s/

LAURIE A KELLEY
02/23/2016

Memorandum

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
OFFICE OF SURVEILLANCE AND EPIDEMIOLOGY
OFFICE OF PHARMACOVIGILANCE AND EPIDEMIOLOGY

DATE: 18 January 2016

FROM: John R. Senior, M.D., Associate Director for Science (Hepatology),
Office of Pharmacovigilance and Epidemiology (OPE)

TO: Billy Dunn, M.D., Director, Division of Neurological Products (DNP)
M. Lourdes Villalba, M.D., Medical Safety Reviewer, DNP
Alice Hughes, M.D., Deputy Director for Safety, DNP
John Marler, M.D., Medical Team Leader, DNP
Sally U. Yasuda, PharmD, Lead Pharmacologist, DNP

VIA: Gerald Dal Pan, M.D. Director, Office of Surveillance and Epidemiology (OSE)
Robert Ball, M.D., Deputy Director, OSE
Mark Avigan, M.D., Office of Pharmacoepidemiology (OPE/OSE)

SUBJECT: Case of fatal liver disorder in an Ukranian woman 46 treated with daclizumab for multiple sclerosis, and other problems; consultation request to OSE sent 7 August 2015; detailed information and attachments received 2 November 2015; further commentary on Avigan responsive consultation of 5 November 2015.

Documents reviewed:

- 1) Consultation request of 7 August 2015
- 2) Documents attached to consultation request, forwarded by M.L. Villalba 2 November 2015
- 3) Consultation response by M. Avigan 5 November 2015
- 4) Report of Hepatic Adjudication Committee (HAC), (b) (4) 27 January 2015
- 5) Investigator's Brochure, DAC HYP, Multiple Sclerosis, 2 April 2015
- 6) Documents submitted to the DARRTS for BLA 761029
- 7) Selected medical literature articles, and other items

The initial consultation request of 7 August 2015 was sent from DNP requesting evaluation by the Office of Surveillance and Epidemiology (OSE) of the liver toxicity profile of daclizumab high yield process (DAC HYP) in patients with multiple sclerosis. It asked for OSE opinion as to what post-marketing measures could be used to minimize risks of autoimmune hepatitis (AIH), given that there were at least 6 cases of AIH, including one fatal case, in the BLA application 761029 submitted by AbbVie on 2/27/2015. It was noted that subsequent to that death on (b) (6), all DAC HP protocols followed very stringent eligibility, monitoring, and stopping criteria, and all cases consistent with drug-induced liver injury resolved after discontinuing drug, with or without corticosteroid treatment. The request mentioned that specific questions can be found on page 4, but no page 4 was sent then (see DARRTS 8/7/2015, Laurie A. Kelley).

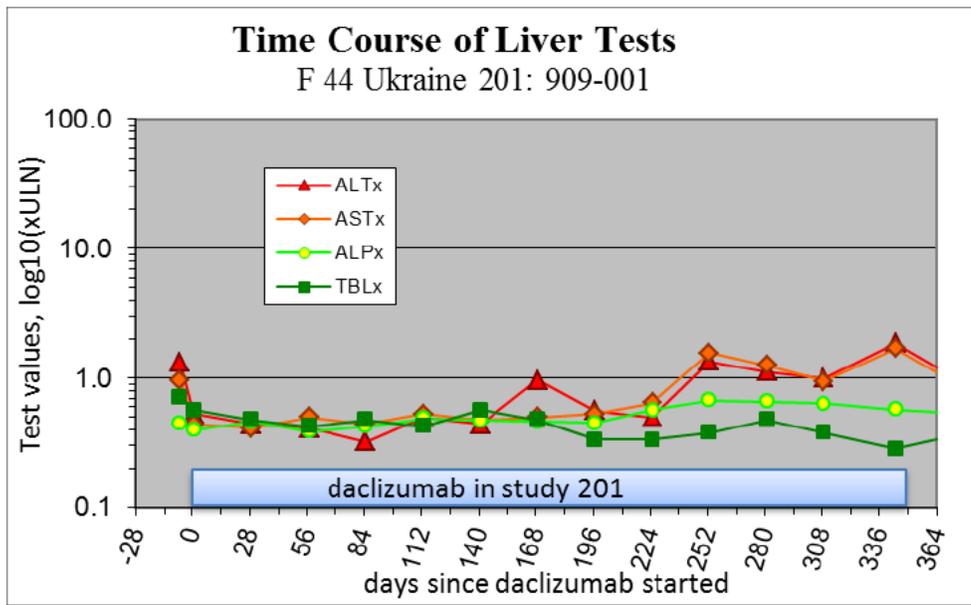
This response is an addendum to the extensive and excellent consultation completed by Dr. M. I. Avigan on 5 November and sent into DARRTS 9 November via Ermias Zerislassie. It reflects my further thoughts and reflections (*in italics*) on the pending review on BLA 761029, and the expected DNP decision in the coming months of 2016. When I first learned of it in mid-August, I had only the front sheet of the consultation request of 7 August sent to OSE, but was asked by the safety reviewer Lourdes Villalba then to look at the serious cases of liver toxicity, especially the fatal case, that she found and was previously found by the HAC consultants to the sponsor (b) (4). Both she and the HAC consultants used an approach to finding and evaluating cases of serious interest in clinical trials based on the eDISH program (evaluation of **D**rug-**I**nduced **S**erious **H**epatotoxicity) developed in 2003-4 in the CDER Office of Pharmacoeconomics and Statistical Science (OPaSS, previous name for OSE). The eDISH program is written in SASIntrNet code by Dr. Ted Guo and was not available to the HAC, but they asked Biogen-Idec to simulate it using JReview, as did Dr Villalba. She called my attention on the fatal case of acute liver failure apparently induced by DAC HYP.

That case was 202:909-001, the first patient enrolled at site 909. In study 202, the death from liver failure was agreed by all to have been probably caused by the DAC HYP. I agreed to look at the case in detail, but found extracting the data from the EDR was exceedingly tedious, and I declined to review the other cases until the sponsor submitted them to Dr. Ted Guo for entry into the eDISH program, which Dr. Villalba requested, and data were received in late October..

The patient in question was a white woman 44 who was started on DAC HYP 300 mg injection at three s.c. sites every 4 weeks in Study 201, the first dose administered (b) (4), (b) (6), then 12 more doses every four weeks until the 13th given on (b) (4), (b) (6).

daclizumab		909-001	treated 205-MS-201									
			F45, White		Site 909, Subject 001							
week	date	central lab	34	34	106	21	Day	ALTx	ASTx	ALPx	TBLx	ALTx/ALPx
scr	(b) (6)	screened	ALT	AST	ALP	TBL						R
0		1st dose	45	33	48	15	-6	1.32	0.97	0.45	0.71	2.9
4		2nd	18	15	42	12	1	0.53	0.44	0.40	0.57	1.3
8		3rd	15	14	49	10	29	0.44	0.41	0.46	0.48	1.0
12		4th	14	17	41	9	57	0.41	0.50	0.39	0.43	1.1
16		5th	11	15	45	10	85	0.32	0.44	0.42	0.48	0.8
20		6th	17	18	52	9	113	0.50	0.53	0.49	0.43	1.0
24		7th	15	16	50	12	141	0.44	0.47	0.47	0.57	0.9
28		8th	33	17	49	10	169	0.97	0.50	0.46	0.48	2.1
32		9th	19	18	48	7	197	0.56	0.53	0.45	0.33	1.2
36		10th	17	22	60	7	225	0.50	0.65	0.57	0.33	0.9
40		11th	46	53	72	8	253	1.35	1.56	0.68	0.38	2.0
44		12th	38	43	70	10	281	1.12	1.26	0.66	0.48	1.7
48		13th last	34	32	68	8	309	1.00	0.94	0.64	0.38	1.6
			63	58	61	6	344	1.85	1.71	0.58	0.29	3.2

(Clinical laboratory data for the liver tests were found in Section 5.3.5.1 of the EDR Life Cycle list, for Study 201 at link from 12.3 (index p 169) to Appendix 16.2, Blood Chemistry section , pages 2206-7 of 3292. Dates on which blood was drawn for tests were calculated from the Study Day figures listed.



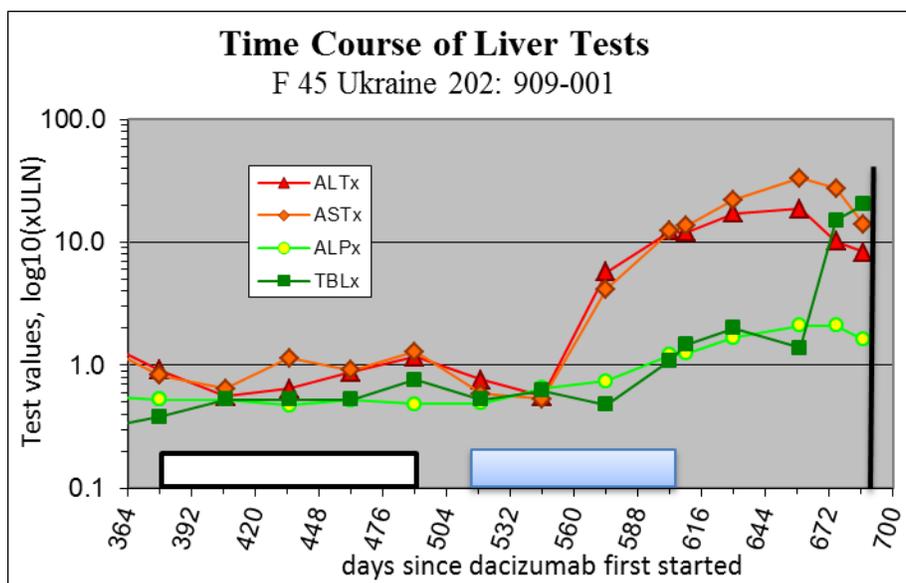
Slight serum ALT increases were reported after injections on (b) (6) (Study Days 253, 281, 344) without reported symptoms or elevation in the serum total bilirubin. The patient agreed to continue into Study 202, and was randomized to receive 5 placebo injections before DAC HYP 300 mg injections were restarted. **A very different response occurred!**

week	date	ALT	AST	ALP	TBL	Day	ALTx	ASTx	ALPx	TBLx
0'	(b) (6)									
0'	placebo #1	31	28	56	48	378	0.91	0.82	0.53	0.38
4'	placebo #2	19	22	56	11	407	0.56	0.65	0.53	0.52
8'	placebo #3	22	39	50	11	435	0.65	1.15	0.47	0.52
12'	placebo #4	30	31	55	11	462	0.88	0.91	0.52	0.52
16'	placebo #5	40	44	51	16	490	1.18	1.29	0.48	0.76
20'	restart DAC	26	20	52	11	519	0.76	0.59	0.49	0.52
24'	DAC #2	19	18	69	13	546	0.56	0.53	0.65	0.62
28'	DAC #3	195	141	79	10	574	5.74	4.15	0.75	0.48
32'	4th DAC 300	419	420	128	23	602	12.32	12.35	1.21	1.10
33'	stop drug	408	461	132	31	609	12.00	13.56	1.25	1.48
36'	hepatitis	582	751	178	42	630	17.12	22.09	1.68	2.00
40'	adm (b) (6)	638	1130	222	29	659	18.76	33.24	2.09	1.38
--	jaundice	344	929	222	317	675	10.12	27.32	2.09	15.10
--'	pred (b) (6)	281	474	172	425	687	8.26	13.94	1.62	20.24
	died	60*	28*	17*	252*	692	1.76	0.82	0.16	12.00

(*local laboratory in (b) (4))

After the 5th injection in Study 202 (b) (6) the patient reported a mild relapse of multiple sclerosis symptoms (b) (6) and was hospitalized 2 days later for methylprednisolone I.V. 1000 mg daily for 3 days (b) (6) with immediate improvement from EDSS 5.0

back to her previously stable 4.0 EDSS level. In hospital she then received another injection (300 mg DAC HYP) (b) (6) and was discharged (b) (6). The next injection (b) (6) caused no apparent effect, but the delayed report in early January of her blood tests drawn at the (b) (6) visit showed a sharp rise in her serum ALT from 19 to 195, accompanied by AST increase from 18 to 141 (upper limit of normal for the central laboratory, 34 international units/liter (IU/L), interpreted by the investigator as a mild adverse effect related to study drug of “increase in transaminase, ALT”. After the (b) (6) injection she was reported a week later again to have transaminase elevations, plus a slight increase in serum bilirubin concentration considered a severe, related adverse effect, and the administration of study drug was stopped (b) (6). The patient was started on treatment with Hepabene, an herbal remedy containing milk thistle extract and other herbs. Despite stopping the study drug, the liver injury progressed and was diagnosed as “reactive hepatitis of unknown etiology” (b) (6) “hepatitis of unknown etiology” (b) (6) treated with TIVORTIN (arginine hydrochloride), pyridoxine, ESSENTIALE (polyenylphosphatidyl choline), and cyanocobalamin (b) (6). Ursocholic acid (URSOCHOL) was added (b) (6) and then when jaundice appeared the diagnosis became “cholestatic hepatitis, jaundice” and treatment was started (b) (6) with Tiotrucolinium, Reosorbilat, Atoxil, No-shpa, IV saline, metoclopramide, furosemide, vitamin C, and she was hospitalized. Prednisone 90 mg in 20 mL saline IV daily was given (b) (6) activated charcoal, spironolactone, famotidine, saline, Hepamerz (ornithine), Csilit, Ringers solution, and Hepamerz, and more TIVORTIN, all continued when she was diagnosed as having autoimmune hepatitis (b) (6) to which were added vitamin B1, saline and glucose, Aroxil, Pettamen, and Dufalact, Torsid, Aminoplasmal Gepa, Lactoprotein C, and finally SoluMedrol 1000 mg daily IV (b) (6). The patient died in liver failure on Sunday evening (b) (6) just 90 days after the last injection of DAC HYP 300 mg.



I confess that I do not know what many of those treatments were, and later the sponsor’s agents also asked questions about them – see case report. In Study 202, the patient was randomized to be given 5 injections of placebo and then received 4 injections of 300 mg DAC HYP), but the investigator was blinded under the protocol to know what she was getting. She also did not know results of laboratory tests until some days later after blood samples were sent to a central

laboratory and results were sent back, according to protocol.) After the patient died (b) (6), the investigator was queried many times by Biogen agents--- Shannon Scanlon: 5/2, 6/23 (17 queries), 8/25 (4), 9/29.10/12(2), and then by Lisa Mccauley on 11/17 (4), 11/21 (8), 12/23, 1/5/2012 (4), 1/11 (6), 1/18 (2), 1/26, 2/14 (2), 3/13 (5), 4/20 (7), 4/24, 5/16 (2), 5/22 (7), 6/27... a total of 83 pages of queries about dates, drug names and spelling, and other apparent discrepancies or clarity lack of entries by the investigator on the case report form (q.v., appended).

As stated above, jaundice was noted (b) (6) and she was re-hospitalized (b) (6) with a diagnosis of cholestatic hepatitis. Ascites was then noted and diagnosis changed to autoimmune hepatitis (b) (6), but testing for the usual markers was negative. Administration of the many drugs and herbal remedies, vitamins, and other products had done nothing to improve or prevent the deterioration. Low dose prednisolone, 90 mg in 20 mL saline I.V, was given daily (b) (6) then 3 days of high-dose methylprednisolone 1000 mg were given (b) (6) before she died on Sunday evening (b) (6) in acute liver failure, with renal and multi-organ failure disseminated intravascular coagulation, and encephalopathy. Autopsy showed what appeared to be fulminant autoimmune hepatitis with post-necrotic multi-lobular cirrhosis, spreading fibrous tissue, convergence of hepatic triads.

From the viewpoint of the investigator, as revealed by entries into the case report in her own handwriting, she obviously did not know what was going on, what liver disease the patient had, much less what to do about it. As responsible treating neurologist, she tried everything she knew to help the patient but nothing worked. She simply stood by helplessly as her patient deteriorated into death, then the next morning watched as the autopsy disclosed a destroyed liver.

The above data listings and graphs were done in late August using Excel, but the extraction of the information from the EDR submission of the BLA was so tedious that I asked Dr. Villalba to request that the sponsor provide data for all patients who were treated with DAC HYP in these studies to Dr. Ted Guo for entry into the eDISH program. This seemed reasonable, since the HAC consultants had already asked Biogen to provide data for their eDISH-like evaluation.

After the death of patient 202-909-001, it was said that changes were made to the protocols of the studies underway, so that results of blood testing would be available before the next dose of DAC HYP was to be given, although it was not clear exactly when the protocols were changed, or by whom. The case also prompted recruitment of the expert hepatology consultants (b) (4) and formation of the HAC in April 2013 (b) (6) after the death).

Everyone who had reviewed the index case 202-909-001 agreed (including the members of the HAC, Dr. Villalba, Dr. Avigan, and me) that the fatal liver injury leading the severe dysfunction and death were probably caused by DAC HYP, but the mechanism was unclear. It was notable that many versions of the “narrative” describing details of the index case were used by the various evaluators, from one page for the HAC (see pages 23-4 of 394 in the (b) (4) report), a concise half-page for the eDISH submission to Dr. Guo and me (see below), and a particularly helpful 9-page summary called a “Subject Narrative” found in the EDR 5.3.5.1\NA, 205MS202 Double-blind study extension, referring in index item 12.2.5 link from page 169 to Section 14.3.3 for Subject Narratives for those with serious adverse events, pages 1995-2003 (of 2020)

that I used in assessing the Excel data shown above. No case report for the patient in Study 201 was in the submission, although it would have shown she was very dutiful in following instructions by attending clinic, receiving injections every 4th Tuesday for a year.

Patient Narrative (for eDISH)
<p>46-year-old woman, history of MS and chronic pyelonephritis on no other meds at the time of the nt. In Study 201, randomized to DAC HYP 300 mg for MS and received 13 doses (b) (6)</p> <p>(b) (6) In Study 201, 4/15 of her labs showed elevations (1.1-1.9xULN) in ALT and AST with ALT (b) (6)</p> <p>ILN at screening. In Study 202, she received a planned 5 doses of placebo (b) (6)</p> <p>(b) (6) followed by 4 doses of DAC HYP 300 mg . On (b) (6) her ALT and AST were 5.7 and (b) (6)</p> <p>respectively with normal bilirubin. She received her third dose of DAC HYP on that day. On (b) (6)</p> <p>AST had increased to 12.3 and 12.4 x ULN and her bilirubin was 1.1 x ULN. She received her last (b) (6)</p> <p>C HYP on that day. She was started on Heptabene. Her transaminases and bilirubin continued to rise. (b) (6)</p> <p>al U/S showed cholestatic changes in the gall bladder. She was diagnosed with hepatitis of unknown (b) (6)</p> <p>anocobalamin, Essentiale, pyridoxine, arginine, and ursodeoxycholic acid were added. She became (b) (6)</p> <p>and was hospitalized. Bloodwork for viral, toxic, metabolic, and autoimmune causes was significant for (b) (6)</p> <p>23 g/L (33-49), PT of 28.5 s (INR 2.8), IgA of 5.21 (0.70-4.0), IgG of 17.9 g/L (5.65-17.65), IgM of 6.77 (b) (6)</p> <p>and IgE of 1042.6 IU/mL (1.3-165.3). A CT of the abdomen showed chronic cholecystitis, chronic (b) (6)</p> <p>and ascites. She was diagnosed with autoimmune hepatitis with possible cirrhosis and portal (b) (6)</p> <p>n. She was treated with multiple medications including methylprednisolone which was started (b) (6)</p> <p>continued to deteriorate and died (b) (6) Her autopsy showed autoimmune hepatitis, (b) (6)</p> <p>pe. The Investigator considered the increased ALT/AST and hepatitis to be related to study drug and (b) (6)</p> <p>hune hepatitis and jaundice not related.(END) (#END#)</p>

*It aroused my curiosity as to why so many similar but different versions of the “narratives” were provided by the sponsor, some quite difficult to find in the BLA submission. Searching through the clinical sections further, I found a 51-page visit-by-visit recording of the 202-909-001 case report not called a narrative but a Patient Profile (in 5.3.5.1 Placebo Study, 205MS202, Subject Profiles, NA, Patient Profiles in which pages 5380-5430 of 5789 described the patients and the investigator better than did the retrospectively summarized narratives. **More instructive yet was the 233-page Case Report for subject 202-909-001 that allowed me to put myself in the shoes and mind of the investigator, Dr. Olena Moroz as she tried to manage the case in real-time (with no unblinding of dosing or retrospective data for the course of the patient’s treatment. From the site locations and investigator profiles, Dr. Moroz clearly was an experienced if not distinguished neurologist, trained as a neurologist in her internship, residency and research fellowship (1999-2005), with thesis work (not published), and many years since 2005 as a senior fellow in neurology at the Ukrainian State Scientific Research Institute of Medical and Social Problems Associated with Diasability ,at Dnepropetrovsk, Ukraine (see the Description of Investigators and Sites, pages 226-8 of 496).***

Comment: The point of going through all this is to emphasize that the investigator on the scene was blinded to what treatment her patient had received and was receiving. She was extensively trained and experienced as a clinical neurologist, but apparently had no idea whatsoever about what may have been going on in the patient’s liver, as indicated by the diagnosis changing from month to month as she died, and the bewildering array of useless treatments administered in vain attempt to slow, stop, or reverse the inexorable process that was destroying her liver. On the day of death, (b) (6) blood tests at a local laboratory showed precipitously lower ALT and AST values, not from improvement but as her last few liver cells were all that remained. It was unclear who was making diagnoses, or was advising her, although it seems likely she had told

study administrators at Biogen of the problems she was having. No matter what label may have been given to the fatal process, it appeared at the end that she suffered a virtual immunological hepatectomy from effects of the daclizumab HYP treatment. Was this immunological destruction of nearly all her hepatocytes initiated by a rogue clone of lymphocytes unintentionally targeted wrongly to attack liver cells? Would earlier recognition of the process as an immunological adverse effect lead to prompt use of methylprednisolone, in addition to stopping DAC HYP administration? We can never know. It is likely that simply finding indicators of liver injury would be of no use unless something could be done about it, so monitoring and REMS would not have protected this patient.

It would be of great interest to obtain from the investigator at site 909, Dr. Olena Moroz, her summary of case 001 as she struggled through the difficult last five months (b) (6). She was functioning not only as an investigator to collect data from the study subject by checking boxes on case report forms for statistical analyses, but also as a medical doctor with responsibility for her patient's life. To whom could she turn for help in managing the insidious and inexorable progression of the liver injury, dysfunction, and failure that probably was initiated by the study drug DAC HYP? She was a trained and experienced neurologist, but had little preparation for management of a liver disorder that she called by different names over that period: elevation of serum enzymes, hepatitis of unknown etiology, hepatitis, cholestatic hepatitis with jaundice, and autoimmune hepatitis. The patient probably did not have different diseases, but one disease process to which various names were attached, and possibly not by her, but by whom? Even the distinguished hepatologists of the HAC more than two years later, with all of the data on unblinded dosing and test results in retrospect had great difficulty in assessing the cause of her liver disorder and gave no opinion as to what might or should have been done about it. Dr. Moroz was blinded as to what treatment her subject was given, or when, and had to rely on laboratory testing done at a distant central laboratory with some days' delay in reporting results back to her. Whatever messages were sent to and received from study managers or other physicians at her center would also be of great interest to see. She tried to do whatever she could to treat the progressing liver problem with a variety of useless herbal, drug, and dietary agents, and simply observed as her patient died in hepatic coma on Sunday evening (b) (6) then stood by the next day as the autopsy revealed her destroyed liver. It would also be of interest to see the subject's patient report for study 201 that was not included in the sponsor's submission.

With respect to the other cases of liver injury discussed by Dr. Avigan in his recent review, and by the HAC 2013-4, and by Dr. Villalba, I have re-plotted all of them using the eDISH program and the data provided to Dr. Guo by the sponsor for 2236 patients, 293 exposed for some time to DAC HYP 300 mg and 1943 to 150 mg per injected dose, as of the 25 June 2015 safety update.

Study 201: 621 subjects to placebo (204), 150 mg (208), or 300 mg (209) for one year
“SELECT” Started 15 February 2008 --- Completed 30 August 2011

Study 202: Continuation or five-month washout and resumption, for one year:
“SELECTION” Started 13 February 2008 --- Completed 3 October 2012
 517 subjects: from placebo (170) to 150 mg (86), 300 mg (84)
 from 150 mg (172): washout (86), continue 150 (86)
 from 300 mg (175): washout (88), continue 300 (87)

Study 203: 410 subjects for long-term extension on 150 mg q. 4 weeks for 6.5 years
“SELECTED” Started 31 March 2010 ---- underway (update to 11/14/2014)

Study 301: 1841 subjects to interferon-β, AVONEX (922) or DAC HYP 150 mg (919), 2-3 years
“DECIDE” Started 11 May 2010 --- Completed 5 March 2014

Study 302: 133 subjects for special study of injection techniques 150 mg DAC HYP q. 4 weeks
“EXTEND” Started 10 November 2011 --- underway (update to 11/14/2014)

Study 303: 597 subjects continuing from 301 on 150 mg DAC HYP q. 4 weeks for 5 years
“OBSERVE” Started 15 February 2013 --- underway (update to 11/14/2014)

Therefore, from these studies of patients with multiple sclerosis, as defined in protocols 201 and 301 mainly, 293 were exposed to 300 mg DAC HYP q. 4 weeks s.c. for varying periods of time, and 1943 patients to 150 mg DAC HYP for varying periods of time. Data for the 2236 patients in the requested format were received by Dr. Guo in late October, entered into the eDISH program in a few days, and have been available to me for review and assessment since early November. From these six studies, three completed and three continuing for long-term on 150 mg DAC HYP every 4 weeks, several patients were identified by the HAC in April 2013 for special attention and detailed evaluation, as reported to the sponsor in detail by (b) (4) in his 394-page review submitted in January 2015, just before submission of BLA 761029 by AbbVie. Most of them were also identified by Dr. Villalba after review of the 120-day safety update sent by the sponsor on 25 June 2015 prior to her request and then referred to Dr. Avigan and me for close evaluation because of possible drug-induced liver injury.

The eDISH submission also found the same subset of patients for hepatology attention, which is not surprising since all used a similar approach to case-finding. I shall not repeat the excellent and careful analyses of those cases done by Dr. Avigan in his 5 November response to the DNP consultation request of 7 August, because I agree with his findings and conclusions. If anyone wants to see the eDISH time course graphs and narratives, I shall send them on request.

As listed by Dr. Villalba, the cases of her major concern were 9 who had autoimmune hepatitis diagnosed or considered after being treated with DAC HYP:

Villalba	HAC	Avigan	JRS/eDISH
Study-Site-Subject			
201 NONE	0	0	0
202 -765- 003	+	UNLK	UNLK
202 -909- 001	+	PROB	VLIK FATAL
203 -506- 011	NA	PROB	PROB
203 -508- 012	NA	PROB	PROB
301 -624- 012	+	POSS	PROB
301 -670- 024	+	UNLK	UNLK
303 -670- 035	NA	PROB	PROB
302 -622- 103	+	POSS	POSS
303 -649- 009	+	PROB	PROB

(Note: NA = not assessed; UNLK = unlikely; VLIK = very likely; POSS = possible; PROB = probable)

Results at site 909/643 (Dr. Olena Moroz, Dniepropetrovsk, Ukraine)

Study 201				Study 202				Study 203
site 909- subject	/2009 date	treatment	(of 48) page		/2010 date	treatment	(of 30) page	
-001	6/02	300	21	*	6/14	WO ^R , 300	13	died
-002	8/20	150	25		8/30	150 →	16	?
-003	10/14	plac	30	*	10/14	150 ^R →	19	?
-004	10/13	300	30	*	10/12	WO ^R , 300	18	?
-005	9/28	plac	29		11/23	150 →	21	?
-006*	10/21	150 ^{RR}	30	*	10/26	WO, 150 ^R	20	?
-007	10/28	150	31		11/03	WO, 150	20	?
-008	10/25	150	31		10/26	150 →	20	?
-010	11/05	150	31		11/02	150 →	20	?
-014	11/23	plac	32		11/25	150 →	21	?
-015	11/23	300	33		11/25	300 →	21	?
-017	11/26	150	33		12/13	WO, 150	22	?
-020	12/21	plac	36		12/27	300 →	23	?

(note: 150 or 300 mg DAC HYP or placebo q 4 weeks s.c.; WO = washout; → =continue;
*case report in submission; ^R, relapse of multiple sclerosis)

Study 301				Study 303	
site 643-	/2011		(of 80)	/2013/4	
-003	6/14	Av30	64		?
-004	5/24	150`	64		?
-005	8/01	150`	64		?
-006*	12/20	Av30 ^R	65	early termination	

(note: Av30 = Avonex 30 µg or 150 =DAC HYP 150 mg q/4 weeks s.c.)

The above table of results at site 909/643 is shown for a reason, to indicate that investigator Olena Moroz was an active, cooperative, and credible investigator, starting 13 subjects in Study 201 and persuading all of them to continue into Study 292, plus 4 more subjects into Study 301. It could not be found easily how many of the 17 continued into long-range Studies 203 and 303. Even more impressive was the precise schedule of visits kept, with subject 201-909-001 showing up faithfully every 4th Tuesday morning for a year. It is evident also that some potential subjects were not: in Study 201: -009, -011, -012, -013, -016, -018, -019; in Study 301: --001, -002.

The data from which these details were taken may be found in the submission, in the reports of Controlled Studies, Randomization schedules, Lists of Investigators and Site Information. Dr. Olena Moroz was a well-trained and competent neurologist, even if not a hepatologist, but she was not supposed to be. Even the three expert hepatologists of the HAC, two years later, with all data unblinded, were unsure about what sort of liver disease she had, and what to do about it.

Why have I made so much of just one case?

*Because it was a very important case that caused the Biogen staff to immediately start changing the protocols to avoid delays in getting laboratory test results before the next dose was given and years later to recruit some very skilled (and probably costly) hepatology consultants of the HAC. The case was important because it showed the dangers of protocol requirements (using a central laboratory, blinded treatment) that perhaps were of value for statistical analyses of efficacy, but disastrous if research subjects became ill and then became patients in urgent need of medical treatment, when blinding and delay in getting laboratory results interfered with proper medical care of a sick patient. Beyond that, protocols did not make provisions for what should be done if adverse reactions occurred, especially potentially serious ones such as liver injury. The sponsor did not expect participating neurologists also to be expert medical diagnosticians, hepatologists or gastroenterologists, etc. --- **nor would be practicing neurologists encouraged to prescribe this drug if approved.** It was not a problem of failure to detect the liver injury, but of learning of abnormalities promptly and of knowing or how to find out quickly what could be done to treat the problem, at least to slow it or prevent worsening. Monitoring, even if done, and enforced by REMS, would be of no use unless results could lead to effective action. By the time the diagnosis of autoimmune hepatitis was made (by whom?) (b) (6), it was within a week of her death and too late even for steroid suppression of the immunological process that was killing her liver and only immediate liver transplant might have saved her, but it was not even considered.*

*Perhaps the most important lesson to be drawn from this case may be that it represents **a new and frightening kind of DILI, where stopping drug administration promptly when liver injury with dysfunction was detected was not enough, as shown by the fact that it didn't work.** We have re-learned in the past few decades that liver has an amazing ability to recover, regenerate lost hepatocytes, after damage or removal --- a lesson somehow known to the ancient Greeks two millennia ago when the myth of Prometheus was articulated, an idea scientifically confirmed by the work on liver transplantation, and voluntary donation of half-livers by donors. Whether the loss of hepatocytes results from resection, from chemical or immunological injury, the liver still is powerfully able to regenerate, recover --- if the rate of damage to hepatocytes can be slowed or stopped, to give regeneration a chance. In this case, nothing effective was done for almost 3 months after liver injury and progressive dysfunction were discovered, and the only potentially*

effective treatment by high-dose methylprednisolone was not started until three days before she died of what appeared to be immunological hepatectomy. It cannot be known, only speculated about, what might have happened if the injury caused by the (b) (6) injection of DAC HYP was promptly reported to the investigator and immediately investigated to see if it was getting worse, and what might be causing it, seeking and getting expert consultation immediately and making the diagnosis so that the only effective treatment known for autoimmune hepatitis ----steroids – might have given. **Was this a preventable death that might be avoided in the future!** Whatever the exact mechanism of this new type of DILI may have been, this unfortunate case may be teaching us a new lesson. The monoclonal antibodies are now a very popular new form of pharmaceutical treatment, but we really don't know much about exactly how they work, or what to do when they affect unintended targets—such as hepatocytes. The death of patient 202-909-001 will not have been totally in vain if we learn from it – so what has been learned?

Dr. Avigan is precisely correct in calling for expert immunological consideration of this case, and what it might teach us about other cases to come. It is understandable that great risks of serious or even fatal hepatotoxicity may be ethically and clinically acceptable when treating patients with malignancies almost certain to kill the patient in the near term, seeking to obtain a few extra months of “progression free survival.” That argument does not have equal strength when it is applied to nasty but chronic, slowly progressing diseases such as multiple sclerosis, pulmonary fibrosis, rheumatoid arthritis, etc. Although not listed in his consultation, he had called attention by email to several very pertinent papers (Rech et al, 2012; Kleinewietfeld, Hafler, 2014; Peiseler et al, 2012; Lapierre, Lamarre, 2015). See also the FDA CBER/CDER document *Guidance for Industry: Immunogenicity Assessment for Therapeutic Protein Products*, issued August 2014 (see Parenky, in References, below).

Dr. Avigan's consultation of 5 November 2015 focussed mainly on review and adjudication of the cases of autoimmune hepatitis identified by Dr. M. Lourdes Villalba, the safety reviewer, of which most had also been considered by the Hepatology experts of the HAC in 2013-2014 (see report by (b) (4), January 2015). As shown above, there was repeated consensus that these cases represented a serious problem, but **what was not addressed was what should or could be done about it if detected.** Just leaving the problem to be discovered by monitoring, which is very or impossible difficult to enforce, even with a required risk evaluation and mitigation strategy (REMS), will not suffice. At present there is no authorization to require complete reporting of what happens to all patients treated, similar to the established required to report on all subjects exposed to a drug under IND rules. Voluntary reporting, while idealistic and to be wished for, has not been complete, and actually is quite rare by prescribing physicians, because it is not in their interest to do so. Reporting adverse effects of prescribed drugs exposes prescribing doctors to time-consuming, unreimbursed additional reporting of details, and more disadvantageous, the possibility of lawsuits by patients or their families, for unfavorable outcomes. Consequently, they just don't report adverse effects, and leave the reporting to others, so that about 95% of cases reported come from patients, pharmacists, and others who do not know or understand the facts and details of the cases necessary to make the often difficult diagnosis of most likely cause. The manufacturing sponsors who are required by law to pass along these factually empty reports are not eager to investigate them either, but focus on promotion and marketing of approved drugs.

So what has all this to do with the questions posed by Dr. Villalba on 7 August?

Question 1: *Please evaluate selected cases of DILI in this application, particularly those in which a diagnosis of AIH was made or suspected (list provided in Attachment 3) and confirm whether or not you think they are related to use of DAC HYP.*

Dr. Avigan in his very erudite review focused particularly on the cases identified by Dr. Villalba (and previously by the HAC), and confirmed her concerns that DAC HYP does appear to cause a rather high incidence of potentially serious (and one fatal) hepatic reactions, many with features of autoimmune-like phenotype, in 15 of the 22 pages of his consultation response. In general, I concur with his evaluations (see page 8, above), and will not repeat them in detail here. However Questions 2, 3, and 4 together received just over two pages in the Avigan consultation, and I should like to expand a little bit on his short replies.

Question 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?*

The response given assumes “that an effective clinical and liver test monitoring program can be instituted to detect DAC HYP-induced liver injuries and manage those events appropriately.” It was conceded that “risk of serious or life-threatening outcomes in some individuals who develop rapidly accelerating liver injury may still not be entirely mitigated.”

I do not accept the proposed assumption that an effective monitoring program can be put into place because of several realities:

- 1) Labeling, and attempts to educate prescribing physicians (and patients) simply don’t work reliably, and are less persuasive than the aggressive advertising and promotional activities of marketing personnel of companies after a drug or product is approved as \safe and effective.**
- 2) Monitoring, even if done as advocated, is not enough. Patient 909-001 had ALT and AST detected in December 2010, five months before she died. Her neurologist did not know what to do with the liver injury detected, did not know what to call it, how to treat it, and simply watched it get worse without doing anything useful. Putting the burden of how to diagnose, what to do, how to treat the detected problem, on the managing neurologist would not help, so monitoring and detection would be useless unless beneficial action was taken.**
- 3) Who is to do the suggested “careful evaluation to ensure that benefits outweigh risks for liver injury”? The practicing neurologist has no basis for making this very difficult and heavy decision when faced with an acutely developing case of serious toxicity to the patient’s liver. That decision should be made elsewhere, by either the sponsor who developed the product or by the FDA, or both.**

- 4) **How can a prescribing neurologist judge “approvability of the agent, as well as make treatment decisions for individual patients”? They simply cannot do so, and are more likely to be influenced or persuaded by the marketing and promotional efforts of the sponsor seeking return on the very costly investment of developing the product.**
- 5) **Who is to decide when high-dose steroid treatment should be started? This was not agreed upon even by the world-famous expert hepatologists of the HAC. Is it even possible that practicing neurologists treating multiple sclerosis can be educated to and beyond that level of expertise? Certainly not.**
- 6) **Therefore, I disagree with the conclusions reached in the Avigan consultaion, and think the response inadequate to protect the patient or the prescribing doctor. More must be done, especially on what to do if abnormal serum transaminases are found and reported to the treating physician.**
- 7)

Question 3. *Do you believe that the risk of DILI with DAC HYP could be effectively minimized with appropriate labeling, with or without a REMS?*

Dr. Avigan provided a non-answer to this question, and doubted if it would work, but then suggested that “regular assessments and monitoring at regularly scheduled appointments as could be established in a REMS are likely to reduce serious outcomes.” Where has this been proved in the current submission? 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, with very few deviations when she came on a Monday or Wednesday, for almost two years, as can be seen from the case report forms filled out by the investigator, Dr. Olena Moroz. Even a REMS depends on voluntary reporting and full cooperation, which experience has shown doesn’t happen.

Educational programs to raise concerns and elevate knowledge about risk of serious harms have to compete with advertising and promotional efforts by marketing personnel seeking in the crowded market to gain a better share for their particular product. Their arguments may be easier to understand and accept by busy practicing neurologists. Would that it were not so, but unfortunately, it is..

Question 4. *What other additional studies/analyses would you recommend that the applicant to conduct prior to or after approval to better characterize the hepatotoxic profile of DAC HYP?*

It was suggested that a “comprehensive approach for HCPs to acquire and report a set of pre-specified data elements for patients with liver injury or other adverse events should be instituted.

This 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.” **This was an idea proposed by me in an informal discussion, but I have recently been told that FDA has no authority to require complete reporting of what happens to all patients to whom a new and dangerous drug is prescribed. The burdens of reporting have been placed on the prescribing neurologist and the patient. The costs and risks involved of being called responsible for causing injury, have been avoided by practicing physicians in general, not just neurologists, and voluntary reporting doesn’t work, not matter how well intended it may be.**

The suggestion that “expert input from a cellular immunologist with expertise in experimental treatment models that affect autoimmunity and tolerance should be sought” is a good idea, but not for practicing neurologists. I agree that we simply do not know enough about using monoclonal antibodies aimed at certain targets but sometimes hit others. In the case 909-001 it was very unfortunate that DAC HYP seems to have generated a close of lymphocytes that attacked her liver cells, and even after its serious adverse effects were detected and administration of the products was, 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. I agree that this drug should not be approved until competent immunological evaluation of the data, the opinions of the sponsor, have been reviewed and assessed.

What Next?

The above opinions were drafted and sent on 3 January 2016 for comment, correction, rebuttal, or any reply, to four members of the DNP senior staff, to four physicians in OSE, and to four experienced medical reviewers in other FDA divisions or offices. As of close of business on 15 January (Friday evening), only three replies of any kind have been received: a critique by Dr. Villalba that I spent too much space and time on the index case 201-909-001, and two short comments from the “outside” medical reviewers that my use of the patient’s case report in the investigator’s own handwriting (202-909-001), provided a very insightful perspective of what the neurologist at the site was thinking and doing. I should say also that I cannot claim to speak for OSE, and that the views and opinions expressed are mine only.

With apologies to the expert hepatologists of the HAC, and to Dr. Avigan, I make these perhaps discordant comments in a spirit of generating discussion and now try to seek a best way forward. **I recommend a Complete Response for BLA 761029**, and very careful soul-searching as to what best DNP might do, realizing that we were asked to assess just the risk of liver toxicity of DAC HYP [REDACTED] ^{(b) (4)} and not make an approval recommendation. Clearly, DAC HYP has other toxicities that have occurred in other organs and tissues. It is very difficult to know where DAC HYP might fit among the 12 other approved agents, all of which are problematical, none curative or even clearly helpful in reversing the disabilities caused by the disease. The sponsor of this BLA chose an easy but perhaps not clinically important measure of primary benefit of just reducing relapse rates, and to compare no treatment (placebo) with very old treatment (their own AVONEX brand of interferon beta, approved in 1996). The results are

underwhelming. I have included among the references listed below several very recent papers in which the authors tried to look at the relative risks of harms and chances of benefit of the various products. It is exceeding difficult to compare results with one drug to another, difficult for just a single pair, but far more so for comparison of all 12 of the approved products, studied by various sponsors at different time, using different subsets of patients under different protocols, especially when the principal aim was to gain market for a particular product.

The most difficult problem of all, even more so than establishing with confidence the likelihood of drug causality, is whether treatment with the drug will do more good than harm in the patients treated after approval. Those patients actually treated are likely to be quite different than subjects carefully selected for study in clinical trials, where the principal motive is to show statistically significant efficacy of at least some modest degree, while avoiding adverse effects by deselection of subjects for inclusion and routine monitoring. The real question is: how many of those treated will show how much benefit (or harm), how soon it will occur, and how likely the effects are really attributable to the drug rather than to something else.

Balancing the chances of benefits and risks of harms to demonstrate new benefit or treatment is not easy to determine from clinical trial data that are skewed and biased by clever protocols to favor benefits and support approval. Although thousands of papers have been written and published on the topic of benefit – risk assessment, there still is no widely accepted method for measuring them quantitatively or consistently. A major problem is that clinical trial protocols are designed to show beneficial effects of treatment, and subjects selected are likely to show them **commonly**, whereas the harmful effects are avoided as much as possible and occur quite **rarely**, especially if serious, so trials designed to show benefits are well powered, but underpowered to show harms significantly, and costs of sufficiently large safety studies are prohibitive. It may take years to discover the true extent of the risks of harms which may be relatively rare, even though they are sometimes very severe in magnitude, unpredictable in when they occur or in whom, and difficult to distinguish from diseases or cause by other agents taken concurrently. This should be very well studied and proved by the sponsor *before* approval, but perhaps also after approval when many more and less well selected and studied patients are treated. The only solution to this quandary would be for the **sponsor of the approved drug to bear the costs and responsibility of tracking what actually does happen to ALL the patients treated**, whether they get the benefits claimed on not, and to determine the actual incidence of unintended effects.

I look forward to seeing the efficacy and safety reviews by Drs. Rodichok and Villalba, and also ask that some additional information be requested from the sponsor. I found the submission very difficult to use for finding information that I wanted, even though I recognize that Biogen is a most experienced developer of new treatments for multiple sclerosis. I do not know how all 12 approved agents can be compared to DAC HYP, which treatment should be used for which patients, when to start and when to stop or switch. These 12 products were approved over a period of 22 years, with different protocols, different sponsors, different criteria for efficacy and safety, different patient subsets, as more has been learned about the disease itself and what should be the aims of treatment. For DAC HYP, under study since 2008 of over 2200 multiple sclerosis patients treated at some time for varying lengths of time with 150 or 300 mg s.c. every 4 weeks for up to 8 years (has any patient made it that far yet?).

Biologics or Drugs previously approved for treating multiple sclerosis

<i>date</i>	<i>product</i> <i>dose, route</i>	<i>ubmission</i>	<i>sponsor</i>	<i>trade name</i>
1. 1993 Jul 23	interferon beta 1b SQ 0.25 mg/d, increase by 0.0625 mg/d q 6 weeks	BLA 103471	Bayer	BETASERON
2. 1996 May 26	interferon beta 1a IM 30 mcg weekly, increase by 7.5 mcg q 3 weeks	BLA 103628	Biogen	AVONEX
3. 1996 Dec 30	glatimer acetate SQ 20 mg daily	NDA 020622	Mylan	COPAXONE
4. 2000 Oct 30	mitoxantrone IV 12 mg/m ² q 3 months – no longer used	NDA 021120	Serano	NOVANTRONE
5. 2002 Mar 7	interferon beta 1a SQ, 22 or 44 mcg 3x/week	BLA 103780	Serano	REBIF
6. 2004 Nov 23	natalizumab IV 300 mg, q 4 weeks	BLA 125104	Biogen	TYSABRI
7. 2009 Aug 14	interferon beta 1b SQ 0.25 mg/d, increase by 0.0625 mg/d q 6 weeks	BLA (b) (4)	Novartis	EXTAVIA
8. 2010 Sep 21	fingolimod PO 5 mg daily	NDA (b) (4)	Novartis	GILENYA
9. 2012 Sep 12	teriflunomide PO 7 or 14 mg daily	NDA 202992	Aventis	AUBAGIO
10. 2013 Mar 27	dimethyl fumarate PO 120 mg daily for 7 days, --- to 240 mg bid	NDA 204063	Biogen	TECFIDERA
11. 2014 Aug 13	pegylated interferon SQ 125 mcg q. 14 days	BLA 125499	Biogen	PLEGRIDY
12. 2014 Nov 14	alemtuzumab SQ twice	BLA 103948	Genzyme	LEMTRADA
(2001 May 5	approved for treating chronic leukocytic leukemia and T-cell lymphoma --- withdrawn US and EU in 2012			CAMPATH)

What exactly is daclizumab HYP?

Daclizumab was the first humanized monoclonal antibody approved, as ZENAPAX (Hoffman La Roche, HLR) in 1997, for preventing rejection of renal transplants. Over following years, other drugs were also approved for that indication, and use of ZENAPAX apparently declined, and the approval to study and use the agent was abandoned by HLR, not because of safety concerns but for dwindling market. Meanwhile many (48 other) INDs, both commercial (9) and research (39) for a wide variety of indications were submitted, including preventing rejection of liver or heart transplants, skin grafts, pancreas transplants, bone marrow transplants, lung transplants, severe asthma, prevention of ulcerative colitis, psoriasis, red cell aplasia, uveitis, type 1 diabetes. Nearly all of the other INDs have been terminated, withdrawn, cancelled, or inactive or are exempt; they all used the HLR daclizumab product Ro 24-7375, also known as anti-TAC.

It appeared that daclizumab was a drug (biologic) in search of a use (and market), and had effects on many types of cells, tissues, diseases. Does the HYP process justify renaming DAC HYP as a brand new drug with a different name?

After IND (b) (4) was granted to the Neurological Institute for Neurologic Diseases and Stroke of NIH (National Institutes of Health) in 2003, then Biogen obtained IND 012120 in 2005 for study of DAC HYP for the treatment of multiple sclerosis, and launched the series of studies being evaluated in this BLA 761029 submitted by AbbVie as co-sponsor. Apparently to clear the field, HLR on 22 March 2010 withdrew its commercial INDs (b) (4) and revoked on 19 February 2015 its BLA (b) (4) just as the current BLA 761029 was being submitted by AbbVie and Biogen. It is also noted that AbbVie sold back to Biogen the ownership of BLA 7619029 on 11 May 2015, acknowledged by Biogen on 12 May 2015.

A Note on Monoclonal Antibodies

Shortly after immune globulin structure was elucidated by Porter and by Edelman (recognized by Nobel Prize 1972), it was quickly discovered that clones of pure immune globulins could be obtained (Kohler and Milstein, 1975; Nobel Prize, 1984) by fusing mouse myeloma and mouse spleen cells from an immunized donor to create a “hybridoma” and generating clones expressing stable and constant proteins with the same amino acid sequence and characteristics, that came to be called monoclonal antibodies (mabs). Other species (chimeric) mabs were then produced, and then humanized mabs, and finally fully human mabs. The products were distinguished by giving them “family” names and targets in 1991-3 by an international group meeting in Geneva to agree upon in 2008 a nomenclature (World Health Organization: International Nonproprietary Names, INN) of terminal stems that indicated what sort of mabs they were:

- | | |
|---------------|--------|
| mouse mab: | -omab |
| chimeric mab | -ximab |
| humanized mab | -zumab |
| human mab | -umab |
- a further modification was added to indicate the therapeutic use for which they were intended:
- | | |
|-------|--------------------|
| tu(m) | -tumor target |
| li(m) | -lymphocyte target |

The first mab approved for human use was muronomab-CD3, a mouse mab marketed as OKT3, ORTHOCLONE by Johnson and Johnson in 1986 for treating autoimmune disorders. Two chimeric mabs abciximab and rituximab were approved in 1994 and 1997 for preventing platelet clumping and non-Hodgkin lymphoma. Then in 1997 the first humanized mab --- daclizumab, ZENAPAX, Roche was approved for reducing the rejection rate of renal transplants. Dac-li-zu-mab therefore was a humanized mab that targeted the CD 25 domain of lymphocytes, and now a HYP variant returns with a new (*and meaningless*) name ZINBRYTA, Biogen, or DAC HYP, (b) (4) for reducing multiple myeloma relapse rates (*and for marketing to distinguish it from ZENAPAX*).

Since there has been an enormous proliferation of mabs, some 50-60 already approved, about half for treating various malignancies, and the others for treating immunological diseases. Over 350 are listed by Wikipedia, and thousands have been produced within the past decade, so the flood of new mabs that are attractive to sponsors seeking new approvals is already underway.

But are we ready to evaluate them for safety? Already approved for treating multiple sclerosis are five versions of interferon beta and two humanized monoclonal antibodies: natalizumab, approved in 2004 for treatment of multiple sclerosis and Crohn's disease as TYSABRI, but also called ANTEGREN, that showed causation of progressive multifocal encephalopathy and had to be restricted; and alemtuzumab, originally approved in 2001 for treatment of lymphatic leukemia and lymphoma under trade name CAMPATH Genenzyme, then renamed LEMTRADA when approved for multiple sclerosis in 2014.

The very difficult task of comparing studies for the 12 drugs approved for treating multiple sclerosis has been undertaken by several authors recently (see Coles; Lycke; Knier et al.; Pawate and Bagnato; Radick and Mehr; Torkildsen et al.; Ziemssen et al., in References below)

The question now is whether a 13th new product is needed, whether it really fills an unmet need, as claimed by the sponsor Biogen, and whether it will do more good than harm in patients to whom it will be prescribed. All of the 12 approved products have safety problems, and none work very well for patients with multiple sclerosis. It would seem to be bad luck to approve a 13th, and just let prescribing neurologists figure out which patients with multiple sclerosis at what stage in their disease, should be treated with which product. That is what the sponsor proposes, and what the Avigan consultation supports. If approved, the patients treated may be quite different than subjects selected for study in clinical trials, where the principal aim was to show statistically significant efficacy of at least modest degree, while avoiding adverse effects by selecting subjects for exclusion and routine monitoring. The real question is: how many of those treated will show how much benefit (or harm), how soon it will occur, and how likely the effects are really attributable to the drug rather than to something else. It may take years to discover the true extent of the risks of rare harms sometimes very severe in magnitude, unpredictable in when they occur or in whom, and difficult to distinguish from diseases or cause by other agents taken concurrently. This should be very well studied and proved by the sponsor before approval, and also after approval when many more and less well selected and studied patients are treated.

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 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.

While these comments are being reviewed, I should like to request that the sponsor be asked to provide a few items that I was unable to find in the submission:

- 1) An electronic copy of the study report for patient **201-909-001** that contains the assessment of her disease severity and duration as she was entered into the study;
- 2) An analysis if the effects of rechallenge on subjects who showed minor elevations of serum transaminases activities during study 201, and whether after being randomized to placebo they tolerated rechallenge or not, compared to those who continued DAC HYP in Study 202;
- 3) A clear statement of exactly how many subjects are still taking DAC HYP 150 q 4weeks in long-term studies 203 and 303, as of the end of 2015, 31 December, and if not why they dropped out. Is study 302 finished now?
- 4) A summary by Dr. Olena Moroz, site 909 investigator, of her view of the course of patient 909-001, and her understanding of it, whom she consulted for advice, and how the various diagnoses were made;
- 5) I should be interested as to how the members of the HAC react to my formulation of the fatal case, and to the investigator-centered approach to evaluation and management, as opposed to the retrospective, unblinded approach they used;
- 6) Request that the FDA group who wrote the guidance on immunogenicity assessment for therapeutic protein products (2014), be asked to consult about this application.
- 7) I shall welcome any comments, objections, corrections, or alternative views to comments made above, will send on request my eDISH analyses of individual cases of interest or copies of any of the references cited.

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(These selected references are listed in alphabetical order by first author, with PubMed numbers also provided, to facilitate looking up the full text of what was published. I have pdf copies of all of them, and will send electronic copies of any upon request.)

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

/s/

JOHN R SENIOR

01/18/2016

Final version, after drafts sent 3 January 2016

HUMAN FACTORS LABEL AND LABELING REVIEW

Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

***** This document contains proprietary information that cannot be released to the public*****

Date of This Review: December 31, 2015

Requesting Office or Division: Division of Neurology Products (DNP)

Application Type and Number: BLA 761029

Product Name and Strength: Zinbryta (daclizumab)* injection
150 mg/mL
*The proper name has not yet been determined, “daclizumab” is used throughout this review as the nonproprietary name for this product.

Product Type: Drug-Device Combination Product

Rx or OTC: Rx

Applicant/Sponsor Name: Biogen Inc.

Submission Date: February 27, 2015

OSE RCM #: 2015-530 and 2015-958

DMEPA Primary Reviewer: Justine Harris, BS, RPh

DMEPA Team Leader: Danielle Harris, PharmD, BCPS

DMEPA Associate Director: Irene Z. Chan, PharmD, BCPS

1 REASON FOR REVIEW

Zinbryta is provided in a 150 mg/mL, single-dose, pre-filled syringe intended for once monthly subcutaneous injection administered by patients, caregivers, or healthcare providers in the home or office setting for the treatment of relapsing forms of multiple sclerosis. AbbVie submitted Human Factors (HF) validation study results, labels, and labeling on February 27, 2015 under BLA 761029. Subsequently, there was a change of ownership of this BLA to Biogen on May 12, 2015. The Division of Neurology Products (DNP) requested that DMEPA review the HF study results and proposed labels and labeling for areas of vulnerability that may lead to medication errors.

2 MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review. The Appendices provide the methods and results for each material reviewed.

Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
Previous DMEPA Reviews	B
Human Factors Study	C
ISMP Newsletters	D
FDA Adverse Event Reporting System (FAERS)*	E - N/A
Other	F – N/A
Labels and Labeling	G

N/A=not applicable for this review

*We do not typically search FAERS for label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

3.1 HUMAN FACTORS STUDY

Based upon the results of the human factors validation study which included an Instructions for Use (IFU) validation, and a supplemental human factors study that evaluated the modifications to the design of the syringe tray and readability of the syringe label, we determined the

prefilled syringe (PFS) can be used safely and correctly when used by patients, caregivers, and healthcare professionals who have the Instructions for Use available.

The HF study consisted of both trained and untrained participants. Although we cannot determine that training makes a significant difference in user performance with this product, we note that participants who received training had fewer use errors than untrained participants and the trained participants had no critical task failures.

We note that 6 untrained participants experienced difficulty removing the needle cover, with one participant receiving a needle stick as a result. In addition, 2 untrained participants did not fully depress the plunger rod, which resulted in a partial dose in 1 participant. We were concerned that removal of the needle cover and the depressing the plunger may require excess force, which may be difficult in this patient population who may have limited dexterity and hand strength. We contacted the Center for Devices and Radiological Health (CDRH) device engineer consultant for their assessment. The consultant responded there was only one complaint during large-scale clinical trials and that from the CDRH perspective, the device constituent of the combination product is designed to fit the majority of the intended user population without problems. Thus, we find this concern adequately addressed.

Four untrained participants failed the step of injecting the medication. Of these, three participants did not inject the full dose and one participant pulled back on the syringe accidentally spilling the medication onto the pad. When the failures were further investigated it was reported that one of the four patients stated that she was instructed to pull back on the plunger by her nurse and did not realize that the injection was not fully completed. Another patient reported numbness in her hands and was unaware that the injection was not complete. One participant was inexperienced in the use of PFS, did not read the IFU, and stated that she was nervous and unsure how to use needles. The final untrained participant did not visually confirm that the medication was fully injected prior to removing the syringe from the pad. We note that the IFU includes a negative statement in Step 6 that reads “Do not pull back on the plunger” prior to instructing users to push the plunger fully. Negative statements have been misinterpreted and require more effort to interpret correctly.¹ In this case, the negative statement precedes the positive action statement. Thus, we recommend removing this statement to minimize the risk for this type of use error.

Seventeen participants (16 untrained and 1 trained) failed to indicate the correct injection site. The reported root causes of these failures were previous injection experience with other devices, not referring to the image in the IFU, or thinking that the injection was to be given IM due to previous experience. The IFU contains text and a diagram of appropriate injection sites; however, we note that the instruction is listed in Step 3 but the injection does not occur until Step 5. We recommend that Step 5 of the IFU is updated to include a first bullet that reminds the user to see Step 3 for proper injection sites.

¹ Institute for Safe Medication Practices. Affirmative warnings (do this) may be better understood than negative warnings (do not do that). ISMP Med Saf Alert Acute Care. 2010;15(16):1-2.

Twenty-two participants (4 trained and 18 untrained) failed the step of pinching the injection site. Root causes noted were prior experience with other devices including autoinjectors, participants thinking that it was not necessary or difficult to pinch the pad for a simulated injection, and not reading or misinterpreting the IFU (participant thought the IFU instructed to pinch, release, then insert needle). The Applicant has updated the IFU to add text to indicate that the user should (b) (4) pinch (b) (4) to help clarify this step. We agree that this revision may help to avoid confusion with this step.

A summary of results from the validation study for the trained and untrained participants are presented in Appendix C.2.

We note that the sponsor intends to include language in the labeling (b) (4)
(b) (4)
(b) (4). Therefore, we recommend revising the proposed statement to read similar to (b) (4)

In addition, the sponsor intends (b) (4)

Our analysis did not identify any new or unique errors specific to this product that are not already seen with similar products utilized in the MS population. We considered our experience with other currently marketed prefilled syringe products utilized in the MS population and determined that further changes to the IFU should be implemented for improved clarity and to minimize the risk for medication errors. However, these changes can be implemented without requiring another HF validation study.

3.2 LABELS AND LABELING

Our review of the Prescribing Information (PI), Medication Guide (MG), and Instructions for Use (IFU) identified areas of vulnerability that can be improved from a medication error perspective. We note the presence of trailing zeros in the statement “150 mg milligrams per 1.0 mL solution” which is found in the *Dosage Forms and Strengths* Section of both the Prescribing Information Highlights and the Full Prescribing Information. We are concerned that trailing zeros can be misinterpreted if the decimal is overlooked (1.0 mL vs. 10 mL) and can lead to ten-fold dosing errors. The statements should be revised to decrease the potential for error. Our review of the carton and container labels identified areas of vulnerability from a medication

error perspective. The strength is not displayed prominently on the principle display panel (PDP) of the carton labeling and should be revised to improve the readability of this important information. A trailing zero is present on the carton side panel and should be removed to prevent misinterpretation. To decrease the risk of wrong route errors, the “For subcutaneous use only” statement should be revised to increase the prominence and readability on the principal display panel (PDP) of the carton labeling and should be added to the container labels. Additionally, a “usual dose” statement should be added to the carton side panel.² We also note that the sponsor proposes (b) (4)

(b) (4)

Furthermore, , the storage instructions on the carton labeling should be the same as that in the PI to clearly designate healthcare provider (HCP) storage vs. patient storage.

4 CONCLUSION & RECOMMENDATIONS

We find the results of the human factors validation study acceptable. However, our review of the HF study results and proposed labels and labeling identified areas that can be improved to increase the readability and prominence of important information, to promote the safe and correct use of the product, and to clarify information. We provide recommendations below. These recommendations can be implemented without requiring validation through another human factors study.

4.1 RECOMMENDATIONS FOR THE DIVISION

A. Prescribing Information Highlights

1. In the *Dosage Forms and Strengths* section, remove the trailing zero from “150 milligrams per 1.0 mL solution” to avoid misinterpretation (1.0 mL vs. 10 mL).
2. In the Dosage and Administration Section contains a statement (b) (4)

(b) (4)

Therefore, we recommend revising the proposed statement (b) (4)

(b) (4)

² 21 CFR 201.55

B. Full Prescribing information

1. In Section 3, *Dosage Forms and Strengths*, remove the trailing zero from “150 milligrams per 1.0 mL solution” to avoid misinterpretation (1.0 mL vs. 10 mL).

2. For Section 2.2, *Important Administration Instructions*, see A.1 above

4.2 RECOMMENDATIONS FOR BIOGEN

We recommend the following are implemented prior to approval of this BLA. These recommendations can be implemented without requiring validation through another human factors study.

A. Commercial (b) (4) PFS Carton

1. The strength is not displayed prominently on the principal display panel. To improve the readability, please increase the prominence by, for example, using bold and/or larger font size.
2. On the side panel, remove the trailing zero ‘Each 1.0 mL single dose Zinbryta’ to avoid misinterpretation of dosage volume.
3. Increase the prominence of the statement “For subcutaneous use only” with bold font or by other means, to decrease the risk for wrong route of administration errors.
4. On the side panel, since the dose is constant, include the “usual dose” information on the labeling.
5. The (b) (4) Zinbryta labeling does not denote the status of this drug product, (b) (4) Please include this information on the labeling.³
6. Add the storage instructions outside the refrigerator that appear in the PI. Include instructions for (b) (4) patient storage
For example:

(b) (4)

³ (b) (4)

B. Commercial (b) (4) PFS Container Label

1. Add the route of administration “ For Subcutaneous Use Only” to decrease the risk for wrong route of administration errors.

C. Instructions for Use

1. We note that the IFU includes a negative statement in Step 6 that reads “Do not pull back on the plunger” prior to instructing users to push the plunger fully. Negative statements have been misinterpreted and require more effort to interpret correctly. Thus, we recommend removing this statement to minimize the risk for this type of use error.
2. We note that in Step 3 of the IFU, there is instruction and diagrams of appropriate injection sites however, the injection does not occur until Step 5. We recommend that Step 5 of the IFU be updated to include a first bullet that reminds the user to see Step 3 for proper injection sites.

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Zinbryta PFS that BIOGEN submitted on May 12, 2015.

Table 2. Relevant Product Information for Zinbryta	
Initial Approval Date	N/A
Active Ingredient	established name pending
Indication	Indicated for the treatment of patients with relapsing forms of multiple sclerosis
Route of Administration	Subcutaneous
Dosage Form	Injection
Strength	150 mg/mL
Dose and Frequency	150 mg injected subcutaneously once per month; the usual sites for subcutaneous injection include the thigh, abdomen, and back of the upper arm.
How Supplied	available in a carton containing a single-dose prefilled syringe providing 150 mg of ZINBRYTA
Storage	<p>Store in the closed original carton to protect from light until ready for injection. Store in a refrigerator between 2°C to 8°C (36°F to 46°F). Do not freeze.</p> <p>Discard if frozen. Once removed from the refrigerator, ZINBRYTA should be allowed to warm to room temperature (about 30 minutes) prior to injection. Do not use external heat sources such as hot water to warm ZINBRYTA. If refrigeration is unavailable, ZINBRYTA may be stored at temperatures up to 30°C (86°F) for a period up to 30 days, protected from light. Do not place ZINBRYTA back into the refrigerator after warming to room temperature. If ZINBRYTA is at room temperature (up to 30°C/86°F) for more than 30 days, it should be discarded.</p>
Container Closure	<p>Prefilled syringe with the needle pre-attached containing a single dose.</p> <p>Each dose of ZINBRYTA is contained in a 1 mL single dose, disposable prefilled syringe made of glass (Type 1) with a (b) (4) rubber plunger stopper and (b) (4) rigid needle shield. The rubber plunger stopper and rigid needle shield are not made with natural rubber latex (b) (4). A 29 gauge, 0.5 inch staked needle is pre-affixed to the syringe. A single prefilled syringe contains 1 mL of solution.</p>

APPENDIX B. PREVIOUS DMEPA REVIEWS

B.1 Methods

On May 19, 2015, we searched the L:drive and AIMS using the terms, daclizumab, and Zinbryta to identify reviews previously performed by DMEPA.

B.2 Results

Our search identified three previous reviews⁴⁵⁶, however, none of the reviews were relevant to this review as the reviews were for evaluation of human factor studies performed on the pen (which is not included in the BLA submission) and a review for the proprietary name Zinbryta PFS.

⁴ Sheppard, J. Human Factors Review for Daclizumab IND 012120. Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2014 MAY 30. RCM No.: 2014-662

⁵ Gao, T. Review of Revised Human Factors Protocol for Daclizumab IND 012120. Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2014 OCT 08. RCM No.: 2014-1897

⁶ Harris, J. Proprietary Name Review for Zinbryta BLA 761029. Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2015 JUN 10. RCM No.: 2015-114367

APPENDIX C. HUMAN FACTORS STUDY

C.1 Study Design

The Human Factors Study Results and IFU submitted on March 3, 2015 were evaluated. Below is a brief overview of the study objectives, description of the study participations, study design, data collection, and data analysis

Study Objective:

A validation test was performed to demonstrate that the intended end user of the PFS can safely and effectively perform critical tasks for the intended uses in the expected use environments. The final production version of the PFS, proposed labeling, and finished goods packaging (complete system) was used to ensure the appropriate level of realism was incorporated into the study design. The study objectives for the validation testing are provided in the table below.

Objective	Description
Primary Objectives	
Performance Assessment	Through observation of the PFS use, identify any tasks in the use process that led to performance failures or difficulties/near misses.
Investigation of performance difficulties or failures	Through targeted discussion with participants, determine causes of any observed performance failures or difficulties/near misses.
Secondary Objective	
IFU Validation	Through observation of the PFS use according to the instructions and targeted discussion, identify any sources of confusion in the instructions.

Study Participants:

Eighty-four (84) participants were enrolled in the study. The following table provides a description of the five distinct user groups.

Participant Type	Trained	Untrained	Total
MS Patients	18	15	33
MS Caregivers	17	18	35
HCPs	N/A	16	16
Total	35	49	84

Training and Training Sessions:

The training provided to study participants for using the PFS in the clinical and usability studies was consistent in regards to the training that will be available in the commercial setting.

Training proposed for PFS includes:

- IFU leaflet (as part of medication guide)

(b) (4)

For trained participants, a 24-hour training delay period was factored into the study design to assess the impact of any associated learning decay.

Methodology and Measurements:

Test participants were asked to complete the user tasks outlined in the study. Subjective feedback was collected throughout the testing session using an in-depth interview, which included comprehension of the IFU. If a participant failed a critical task, they were brought back for a repeat assessment 48 hours later. The purpose of the repeat assessment was to determine if use errors were a result of first time use and that repeat uses led to improved performance.

User Tasks Evaluated in Summative Study and Criticality Designation:

IFU Step/Task	User Task/Function	Failure Effect from uFMEA	Task Rating at Summative Study	New Rating After Summative
Section 2: Preparing for Injection				
Step 1	Place supplies and wash hands	Minor Infection	Desirable	Essential
Step 2	Check pack and prefilled syringe (Check the medication)	No Dose/Partial Dose Minor Injury Minor Infection	Essential	Essential
Section 3: Giving the Injection				
Step 3	Choose (and disinfect) injection site	No Dose/Partial Dose Minor Injury Minor Infection	Essential	Essential
Step 4	Firmly remove needle cover	No Dose/Partial Dose Minor Injury Minor Infection	Critical	Essential
Step 5	Prepare injection site (pinch the skin)	No Dose/Partial Dose Minor Injury Minor Infection	Essential	Essential
Step 6	Inject medication (by inserting needle and push the plunger all the way down and hold the PFS at a 45-90 degree angle to the injection site)	Major Infection (most severe)	Critical	Critical
Step 7	Remove the PFS from the injection site (Care for injection site)	Moderate Injury (most severe)	Essential	Critical
Section 4: After the Injection				
Step 8	Disposal (Throw away PFS device in sharps container; do not recap)	Minor Injury	Desirable	Essential

C.2 Results

A summary of results from the summative study for the trained and untrained participants are presented below:

IFU Step/Task	User Task/Function	Task Rating	Number of Task Failures (Trained)	Number of Task Failures (Untrained)
Preparing for Injection				
Step 1	Place supplies and wash hands	Essential ^a	1	11
Step 2	Check pack and prefilled syringe (Check the medication)	Essential	2	20
Giving the Injection				
Step 3	Choose (and disinfect) injection site	Essential	1	18
Step 4	Firmly remove needle cover	Essential ^a	0	6
Step 5	Prepare injection site (pinch the skin)	Essential	4	18
Step 6	Inject medication (by inserting needle and push the plunger all the way down and hold the PFS at a 45-90 degree angle to the injection site)	Critical	0	4
Step 7	Remove the PFS from the injection site (Care for injection site)	Critical ^a	0	3
After the Injection				
Step 8	Disposal (Throw away PFS device in sharps container; do not recap)	Essential ^a	2	18

Supplemental Human Factors Study

Because of feedback received on the participants having difficulty removing the syringe from the tray and the readability of the syringe label, a supplemental human factors study was done to evaluate modifications to the tray and the syringe label.

Results of Supplemental Human Factors Study:

All participants were able to remove the syringe from the tray with little or no difficulty. All participants were ultimately able to read the lot number and expiration text for the OCR-B7 point, OCR-B 8 point and Tahoma 7 point labels and therefore, are considered viable options.

Conclusions based on results of formative and validation studies:

The PFS, labeling, and IFU have been found to be reasonably safe and effective for the intended end users, its intended uses, and use environments. Because of observations made during the summative study, modifications to the IFU will be implemented; however, since these modifications are minor in nature, a follow-up IFU validation is not recommended.

APPENDIX D. ISMP NEWSLETTERS

D.1 Methods

On June 24, 2015, we searched the Institute for Safe Medication Practices (ISMP) newsletters using the criteria below, and then individually reviewed each newsletter. We limited our analysis to newsletters that described medication errors or actions possibly associated with the label and labeling.

ISMP Newsletters Search Strategy	
ISMP Newsletter(s)	(Acute Care, Community and Nursing)
Search Strategy and Terms	Match Exact Word or Phrase: daclizumab

D.2 Results

Our search yielded no results.

12 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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

/s/

JUSTINE HARRIS
12/31/2015

IRENE Z CHAN on behalf of DANIELLE M HARRIS
12/31/2015

IRENE Z CHAN
12/31/2015

MEMORANDUM

**DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH**

CLINICAL INSPECTION SUMMARY

DATE: November 17, 2015

TO: Laurie Kelley, PA-C, Regulatory Health Project Manager
Lawrence Rodichok, Medical Reviewer
Division of Neurology Drug Products

FROM: Antoine El-Hage, Ph.D.
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

THROUGH: Susan Thompson, M.D.
Team Leader
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

Kassa Ayalew, M.D., M.P.H.
Branch Chief
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

SUBJECT: Evaluation of Clinical Inspections

BLA: 761029

APPLICANT: AbbVie/Biogen

DRUG: Daclizumab
NME: Yes

THERAPEUTIC CLASSIFICATION: Standard Review
INDICATION: Treatment of subjects with relapsing forms of multiple sclerosis
CONSULTATION REQUEST DATE: May 13, 2015
DIVISION ACTION GOAL DATE: December 30, 2015
PDUFA DATE: February 25, 2016
INSPECTION SUMMARY DUE DATE: January 10, 2016

I. OVERALL ASSESSMENT OF FINDINGS AND GENERAL RECOMMENDATIONS

Six clinical investigator sites were inspected in support of this BLA application. The inspection of three clinical investigators listed below revealed regulatory violations. The final classification for Drs. Nadji and Centonze sites are Voluntary Action Indicated (VAI) because of protocol deviations and inadequate record keeping. The pending classification for Dr. Francesco is Voluntary Action Indicated (VAI) because of minor protocol deviations and inadequate record keeping. The final classification for Dr. Dufek is No Action Indicated (NAI), and the pending classification for Drs. Selmaj and Zielinski are No Action Indicated (NAI). The pending classifications are based on preliminary communication with the ORA investigators. A summary addendum will be generated if conclusions change upon receipt and review of the EIRs.

Overall, while the inspectional findings represent observed regulatory deficiencies, these findings are unlikely to have a significant impact on data acceptability. In summary, the study data generated from these clinical sites are considered acceptable and may be used in support of the pending application.

Additional Information:

The EMA shared with OSI their inspectional findings/results of two clinical site inspections for Dr. Conger Nadji In Serbia and Dr. Okinak in Russia ; these two clinical sites inspected by EMA also enrolled subjects in Protocol 205-MS-301. The inspections by EMA for Dr. Conger Nadji in Serbia and Dr. Okinak in Russia did not reveal major GCP violations.

II. BACKGROUND:

The applicant submitted data primarily generated in foreign countries to support approval for the treatment of multiple sclerosis; a common neurological disease affecting over 1 million people worldwide.

Daclizumab High Yield process (DACHYP) is a humanized IgG1 monoclonal antibody specific for the alpha subunit (CD25) of the human high-affinity interleukin -2(IL-2) receptor. A completed phase 2 study demonstrated the potential of daclizumab to reduce MS disease activity more than interferon beta alone. The current trials were designed to test the hypothesis that DAC HYP monotherapy was superior to interferon beta-1a monotherapy for reducing MS disease activity.

The Applicant-sponsored two pivotal Protocols 205-MS-301 and 205-MS-201 which were submitted in support of the pending application. The studies submitted in support of the pending BLA compared daclizumab (sc) administered once every four weeks compared to interferon beta-1 injection once weekly in treatment-naïve patients with RRMS who had recent MS disease activity. The review division elected to inspect only Study 205-MS-301.

Protocol Study 205-MS-301: “Multicenter, Double-Blind, Randomized, Parallel-Group, Monotherapy, Active-control Study to determine the Efficacy and Safety of daclizumab High Yield Process (DACHYP) versus Avonex (Interferon Beta-1a) in Patients with Relapsing-Remitting Multiple Sclerosis”.

Protocol 205-MS-301 was a multicenter, double-blind, randomized, active –control, parallel-group study designed to evaluate the efficacy and safety of DAC HYP versus IFN beta -1a in patient with RRMS. Approximately 900 subjects with relapsing-remitting multiple sclerosis (RRMS) were randomized at approximately 245 sites around the world. Subjects were randomized in a 1:1 ratio into the following groups:

Group 1: Approximately 900 subjects, DAC HYP 150mg SC once every 4 weeks plus Avonex placebo (A-PLC) IM once weekly for 96 to 144 weeks

Group 2: Approximately 900 subjects, IFN beta-1a IM injections 30 mcg once weekly plus DAC HYP placebo (D-PLC) once every 4 weeks for 69 to 144 weeks.

Subjects’ eligibility was determined within four weeks prior to randomization at the Baseline visit. Eligible subjects reported to the site to undergo study assessments at the Baseline Visit and every four weeks during the study. Subjects who prematurely discontinue study treatment before Week 140 continued in the study on a modified visit schedule.

The primary objective of Study 205-MS-301 was to test the superiority of DAC HYP compared to IFN beta-1a in preventing MS relapse in subjects with RRMS. The primary endpoint was the annualized relapse rate (ARR).

The review division requested inspection of the six clinical investigators noted below because data from the studies are considered essential to the approval process. These sites were targeted for inspection due to 1) enrollment of a relatively large number of subjects, 2) the results drove the efficacy outcome at the site, 3) the need to determine if sites conducted the trials ethically and were in compliance with GCP regulation and local requirements (Eastern Europe), and 4) there was insufficient domestic enrollment in the U.S. compared to foreign enrollment to justify domestic inspection. It is for these reasons that it is critical that international sites were included in the inspection. The sites below were identified to be of interest to the review team.

Dr. Centonze/Site 459 high dropout rate; Dr. Patti/Site 453 large number of excluded; Dr. Nadji/Site 670 high enroller; Dr. Dufek/Site 659 high dropout rate; Dr. Selmaj/Site 604 large number of excluded subjects (10) plus the largest number of enrolled subjects in both Protocols 201&301; the division would like to know if there was an overlap of enrollment of subjects in both studies at the same time. Dr. Zielinski/Site 611 had a high dropout rate.

II. RESULTS (by protocol/site):

Name of CI, Location, and Site #	Protocol and # of Subjects Randomized	Inspection Dates	Final Classification
Krzysztof Selmaj, M.D. Aodz, LODZKIE, 90-153 Poland Site #604	MS-301 Number of subjects: 54	10/12- 16/2015	Pending (preliminary classification NAI)
Michal Dufek, M.D. Brno, 656 91 Czech Republic Site #659	MS-301 Number of subjects: 23	7/27-31/2015	NAI
Congor Nadj, M.D. Novi Sad, 21000, Serbia Site #670	MS-301 Number of subjects: 41	8/3-7/2015	VAI
Tomasz Zielinski, M.D. Katowice, SLASKIE, 40650, Poland Site # 611	MS-301 Number of subjects: 40 subjects	10/6-9/2015	Pending (preliminary classification NAI)
Francesco Patti, M.D. Multipla, Via Santa Sofia Catania, 95123 Italy Site #453	MS-301 Number of subjects 40	7/27-30/2015	Pending (preliminary classification VAI)
Centonze Diego, M.D. Roma, ROMA 00123 Italy Site# 459	MS-301 Number of subjects 14	8/3-5/2015	VAI

Key to Classifications

NAI = No deviations

VAI = Deviation(s) from regulations

OAI = Significant deviations from regulations. Data found unreliable.

Pending = Preliminary classification based on e-mail communication from the field; the Establishment Inspectional Report (EIR) has not been received from the field and complete review of EIR is pending. An inspection summary addendum will be generated if conclusions change upon receipt and review of the EIRs.

1. Krzysztof Selmaj, M.D.**Aodz, Lodzkie 90-153, Poland**

- a. What Was Inspected:** At this site, a total of 69 subjects were screened, 14 subjects were reported as screen failures, 55 subjects were randomized into the study, and one

subject was transferred to another site. Forty one subjects completed the study and follow-up at this site.

The medical records/source data for 25 subjects were reviewed and compared to data listings. The review included drug accountability records, drug dispensing records, inclusion/exclusion criteria, vital signs, IRB records, sponsor correspondence, and adverse events. Source documents for 25 subjects verified eligibility criteria, protocol compliance, and the use of concomitant medications. The source documents were compared to case report forms and data listings including primary efficacy endpoints and adverse events listings. Review of the informed Consent Documents for all subjects reviewed, verified that subjects signed informed consent prior to enrollment.

- b. General Observations/Commentary:** At the conclusion of the inspection, no Form FDA 483 was issued to Dr. Selmaj. In general, the medical records were found to be in order, organized and the data verifiable. There were no unreported deaths and no evidence of under-reporting of adverse events. There were no known limitations to the inspection.
- c. Assessment of Data Integrity:** Overall the data generated by this site are considered reliable and may be used in support of the pending application.

**2. Michal Dufek, M.D.
Brno, 656 91 Czech republic**

- a. What Was Inspected:** At this site a total of 25 subjects were screened, seven subjects were reported as screen failures, two subjects were reported as screen failures, 23 subjects were randomized into the study, two subjects voluntarily withdrew, and one subject discontinued due to bladder colic. Twenty subjects completed the study, and 18 subjects continued on the extension phase of the study. Review of the Informed Consent Documents, for the majority of subjects records reviewed, verified that all subjects signed informed consent forms prior to enrollment.

The medical records/source documents for 12 subjects were reviewed including drug accountability records, vital signs, IRB files, laboratory results, inclusion/exclusion criteria, prior and concomitant medications, informed consent documents, patient diaries, and adverse events reporting. The field investigator compared the source documents/primary and secondary endpoints and adverse events reporting to the data listings for primary efficacy endpoints, and no discrepancies were noted.

- b. General Observations/Commentary:** At the conclusion of the inspection, no Form FDA 483 was issued to Dr. Dufek. The ORA investigator found a discrepancy in that the wrong kit was distributed to Subject #05. The sponsor allowed the subject to continue on the study. The inspectional observation was discussed with the clinical investigator who agreed with the finding to be an error by the pharmacist.

In general, the medical records reviewed were found to be in order, organized, and the data verifiable. There was no evidence of under-reporting of adverse events to the sponsor or the agency. There were no known limitations to the inspection.

- c. **Assessment of Data Integrity:** The data in support of the clinical efficacy and safety at this site are considered reliable and may be used in support of the pending applications.

**3. Congor Nadj, M.D.
Novi Sad 21000, Serbia**

- a. **What Was Inspected:** At this site, a total of 42 subjects were screened, one subject was reported as a screen failure, 35 subjects completed the study, and 32 subjects continued on the extension phase of the study. Review of the Informed Consent Documents, for all subjects reviewed, verified that subjects signed informed consent forms prior to enrollment.

The medical records/source data for 30 subjects and MRI and EDSS scores were reviewed; the records for 19 subjects verified vital signs and laboratory results; the records for 11 subjects verified inclusion/exclusion criteria, concomitant medications drug accountability records, informed consent documents, IRB records, and three subjects' diaries. The source documents for the majority of subjects were compared to data listings for primary efficacy endpoints and adverse events reporting.

- b. **General Observations/Commentary:** At the conclusion of the inspection, no Form FDA 483 was issued to Dr. Nadj. However, the ORA investigator found minor protocol deviations and inadequate record keeping. The inspectional observations were discussed with the clinical investigator and his staff and included, but were not limited to the following:
 1. The ORA investigator reported that Subject #017 received concomitant medication Synopen topical chloropyramine 1% for rash. The use of concomitant medication was not reported on the e-CRF and subsequently not reported to the sponsor.
 2. The ORA investigator emphasized the importance of ensuring the study information documented on the source document and the e-CRFs are accurate and complete. Any changes made to the original entries must be made with across out errors with a single line, initialed, and dated. The source must be kept and not obliterated or destroyed.
 3. Subject #015 EDSS score for Visit 3 was recorded on the source document as 3.0 while a score of 1.5 was entered on the-CRF and the data listings submitted to FDA.

The clinical investigator verbally acknowledged the inspectional observations in which he agreed with the findings and stated that he will address the discussed findings in his future studies. OSI finds his response acceptable.

There were time limitations to the inspection due to the need for translation. There were no unreported deaths and no evidence of under-reporting of adverse events at this site.

- c. Assessment of Data Integrity:** Although minor deviations were noted at this site, the findings appear to be isolated instances, and it is unlikely that these findings would significantly impact the outcome of the study. Overall, the data submitted in support of the clinical efficacy and safety is considered reliable and may be used in support of the pending applications.

4. Tomasz Zielinski, M.D.
Katowice, SLASKIE Poland

- a. What Was Inspected:** At this site, 49 subjects were screened, nine subjects were reported as screen failures, 40 subjects were enrolled, and 31 completed the study and continued on the study. An audit of 20 subjects' record was reviewed.

The medical records/source data for 20 subjects were reviewed, which included, but were not limited to, informed consent documents, vital signs, IRB and monitoring correspondence, subjects screening log, protocol compliance, inclusion/exclusion criteria, drug accountability records. Source documents were compared to case report forms and to data listings including primary efficacy endpoints and adverse event reporting. No evidence of inaccuracies was found.

- b. General Observations/Commentary:** At the conclusion of the inspection, no Form FDA 483 was issued to Dr. Zielinski. In general, the medical records were found to be in order, organized, and the data verifiable. There was no evidence of under-reporting of adverse events. There were no known limitations to the inspection.
- c. Assessment of Data Integrity:** The study appears to have been conducted adequately, and the data generated at Dr. Zielinski's site are considered reliable and may be used in support of the pending application.

5. Patti Francesco M.D.
Sofia Catania,95123 Italy

- a. What was inspected:** At this site, a total of 49 subjects were screened, 9 subjects were reported as screen failures, and 40 subjects were randomized, and 28 subjects completed the study.

The medical records/source documents for 13 subjects enrolled were reviewed, which included, but were not limited to, drug accountability records, informed consent documents, vital signs, diary assessments, evaluation of EDSS scores, ECG, IRB files, inclusion/exclusion criteria, study procedures, number of relapses, randomization, monitoring procedures, laboratory results, use of concomitant medications, and sponsor correspondence. Source documents were compared to CRFs and data listings, to include primary efficacy endpoints and adverse events.

- b. General Observations/Commentary:** At the conclusion of the inspection, no Form FDA 483 was issued to Dr. Patti. However, the field investigator discussed with the

clinical investigator the listing of concomitant medications methylprednisolone and Lyrica for Subject 453003, and the completion of MRI for at least three subjects out of window scheduled visits according to the protocol. With the above exceptions, the medical records reviewed were found to be in order, organized, and the data verifiable. There were no deaths and no evidence of under-reporting of adverse events. There were no known limitations to the inspection.

- c. **Assessment of Data Integrity:** The data generated in support of the clinical efficacy and safety at Dr. Patti's site is reliable and may be used in support of the pending applications.

**6. Diego Centonze, M.D.
Roma, 00123 Italy**

- a. **What was inspected:** At this site, a total of 17 were screened, three subjects were reported as screen failures, 14 subjects were enrolled, and 8 subjects completed the study.

The complete medical records/source documents for 14 subjects were reviewed, which included, but were not limited to MRI, EDSS scores, informed consent documents, concomitant medications, drug accountability records, vital signs, IRB files, laboratory results, inclusion/exclusion criteria, use of concomitant medications, and diary assessments. The source documents for the majority of subjects were compared to case report forms and to data listings and adverse events reporting.

- b. **General Observations/Commentary:** At the conclusion of the inspection, no FormFDA 483 was issued to Dr. Centonze. Our investigation noted minor protocol deviations which were discussed with the clinical investigator and his staff and included the following:

Protocol violations:

The ORA investigator reported that Subject #45901 received the concomitant medication Maalox and Subject 3459004 received acyclovir and Laroxyl. The uses of concomitant medications were not recorded on the e-CRF and subsequently were not reported to the sponsor.

In addition, three subjects experienced adverse events which were not recorded on the CRFs and were not included in the data listings:

Subject #459003 experienced drowsiness

Subject #459004 had a cold sore and herpes

Subject #459014 reported pharyngitis

The clinical investigator made no comments regarding the inspectional findings during the exit interview.

The medical records reviewed disclosed no adverse findings that would impact the reliability of the data. In general, the records reviewed were found to be in order

except for the above noted observations. There were no known limitations to this inspection.

- c. **Assessment of Data Integrity:** Although minor deviations were noted at the above site, the findings appear to be isolated instances, and it is unlikely that these findings significantly impacted the outcome of the study. Overall the data generated at this is considered acceptable and may be used in support of the pending application.

7. RESULTS-OTHER

The clinical sites of Drs. Conger Nadji, Novi Sad, Serbia, and Miroslav Odinak, St. Petersburg, Russian Federation were selected and inspected independently by the European Medicine Agency (EMA) and enrolled in Protocol 205-MS-301. The same protocol was inspected by FDA. The EMA summarized the inspections noting that there was no critical finding. The major and minor findings noted by EMA ranged from isolated minor protocol deviations, IRB/IEC membership issues, use of concomitant medication, conduct of the trial, quality of source data, unreadable ECGs, and minor documentation issues. The EMA concluded that despite the findings, the data generated at the two sites were reliable and suitable for assessment. After review of the EMA's inspection report regarding the conduct of Protocol 205-MS-301 at Drs. Nadji's and Odinak's sites, OSI is in agreement that the findings noted at these sites appeared to be isolated examples and are unlikely to adversely affect safety or efficacy assessments. The EMA inspectional findings/results were communicated to OSI.

{See appended electronic signature page}

Antoine El-Hage, Ph.D.
Good Clinical Practice Assessment Branch
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This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

ANTOINE N EL HAGE
12/02/2015

SUSAN D THOMPSON
12/02/2015

KASSA AYALEW
12/02/2015

**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology**

Date: 05 November 2015

To: Billy Dunn, MD, Acting Director,
Division of Neurology Products (DNP)
Alice Hughes, MD, Deputy Director for Safety (DNP)
Lourdes Villalba, MD, Medical Officer, DNP
Sally Yasuda, Ph D, Lead Pharmacologist, DNP
John Marler, MD, Medical Officer, Team Leader, DNP

From: Mark Avigan, MD, CM
Associate Director, Critical Path Initiatives
& Hepatologist,
Office of Pharmacoepidemiology (OPE)
Office of Surveillance and Epidemiology (OSE)

CC: John Senior, MD, Associate Director, OPE
Robert Ball, MD, Deputy Director, OSE
Gerald Dal Pan, MD, Director, OSE

Drug Name: Daclizumab High Yield Process (DAC HYP)

Formulation: S/C [REDACTED] ^{(b) (4)} humanized monoclonal IgG1 Ab
BLA Number: 761029

Applicant/sponsor: Biogen MA Inc., AbbVie Biotherapeutics Inc.

Issue: Assessment of liver toxicity profile of DAC HYP in the clinical development program for remitting-relapsing multiple sclerosis

INTRODUCTION

In a request dated 07 August 2015, DNP has asked for consultation by a hepatologist to evaluate the hepatotoxic risk of daclizumab in the clinical development program of daclizumab high yield process (DAC HYP; Biogen MA, AbbVie Biotherapeutics) for remitting-relapsing multiple sclerosis (RRMS). In the clinical trials of this product, there were cases of daclizumab-associated serious liver injury. In addition, a range of biochemical elevations of serum liver transaminases were noted in some study subjects.

In some instances these abnormalities were accompanied by increases of bilirubin. DAC HYP is a humanized monoclonal IgG1 antibody raised against the alpha subunit of the human high affinity Il-2 receptor (Il-2R) [CD25]. It has been developed for the treatment of relapsing-remitting multiple sclerosis (RRMS) in a subcutaneously administered formulation. In the clinical development program, cases of serious liver injury were observed. These were marked by acute rises of serum ALT / AST that in some instances were also accompanied by elevations of bilirubin and/or other measures of liver dysfunction. It is notable that some cases of DAC HYP occurred only after long-term dosing with the antibody and others despite a significant delay since the last s/c administration of the Il-2 receptor inhibitor. Although there was heterogeneity in the clinical presentation and temporal characteristics of these liver injury cases, concern surrounding a clinically significant hepatotoxic potential of DAC HYP in Multiple Sclerosis patients is raised by the following observations. 1. There has been a consistent imbalance in the percentages of treatment-associated liver injury cases in study subjects randomized to receive the monoclonal antibody vs placebo or an active comparator (IFN- β -1a), 2. At least 7 cases of clinically significant liver injury were marked by autoimmune features raising a concern that a potential unintended consequence of treatment with DAC HYP in some patients is induction of autoimmune liver injury by anti-CD25 inhibition of regulatory T cell suppression. DAC HYP –induced autoimmune organ injury is further supported by an adverse event profile that also includes cases of treatment-associated colitis and a range of skin reactions. 3. One case of fatal autoimmune hepatitis occurred in a study subject who received DAC HYP. The sponsor’s Hepatic Adjudication Committee (HAC) comprised of 3 experts adjudicated this case as ‘probable’ in its causal association with exposure to the monoclonal antibody treatment. 4. Other cases of DAC HYP linked liver injury in the drug development program have been adjudicated as ‘Likely’ or ‘Probable’ in their causal association with the drug by the HAC. A review of these cases together with a request to respond to a series of questions surrounding the assessment of hepatotoxic risk associated with this agent identified in pre-approval development program of DAC HYP has been submitted by the DNP review team for my review as a hepatologist. I have been asked to provide a written summary of the key points in my assessment.

BACKGROUND

DAC HYP is a humanized monoclonal IgG1 antibody raised against the alpha subunit of the human high affinity Il-2 receptor (Il-2R) [CD25]. It inhibits functions mediated by CD-25 and Fc directed functions such as ADCC. A rising number of T-cell targeted therapies have been developed to treat particular neoplastic diseases. Many of these are intended to increase immune reactivity of polyclonal T-cells against tumor cells through inhibition of the checkpoint regulatory molecules CTLA-4 or PD-1 or other cell surface proteins that modulate cell surface interactions between the immunocytes and target cells. Although these therapies are designed to increase the direct or indirect killing of tumor cells by polyclonal T-cells, the promotion of auto-reactive cells has been associated with a number of different unintended autoimmune organ injuries. As illustrative examples, ipilimumab, a monoclonal antibody that blocks CTLA-4 interactions is indicated for the treatment of unresectable or metastatic melanoma, has a safety profile which includes

severe colitis, sometimes associated with intestinal perforation, serious skin reactions, including SJS/TEN, clinically serious autoimmune hepatitis that can result in liver failure, and a variety of autoimmune endocrinopathies. nivolumab, an Ig-G4 monoclonal PD-1 inhibitor for treatment of metastatic melanoma or non-small cell lung carcinoma, has a similar autoimmune safety profile that includes clinically serious colitis, immune-mediated pneumonitis, nephritis, a number of endocrinopathies and autoimmune hepatitis. Treatments designed to alter T-cell function have also been developed to treat a number of auto-immune diseases, including MS. Generally, they are intended to reduce activities of immunocytes that have a direct role in damaging different tissues in conjunction with the autoimmune disease phenotype. A subset of the approved disease modifying treatments to eliminate or inhibit T-cells that target the myelin sheath in relapsing MS have paradoxically been associated with idiosyncratic autoimmune reactions, in some treated patients. These include pegylated and non-pegylated IFN- β 1a, IFN- β 1b, glatiramer acetate and alemtuzumab [In the spectrum of organ involvement pegylated and non-pegylated IFN- β 1a, IFN- β 1b and glatiramer acetate have been linked to autoimmune liver injuries]. It is also notable that some of the other agents currently indicated to treat MS including fingolimod and natalizumab have also been associated with idiosyncratic DILI, albeit without evidence of treatment-induced systemic or serological features of autoimmunity.

DAC HYP clinical program: Immune/auto-immune AE signals across organ systems

In conjunction with the liver signal in the DAC HYP development program for RRMS, a number of other organ injury signals were also observed in the sponsor's clinical studies (see Table 1, below). These have been synopsised in the Summary of Clinical Safety submitted to FDA by the sponsor on February 27, 2015 (Section 2.7.4). In the cumulative DAC HYP serious adverse event clinical trial experience accrued until the submission (n=1,785, p.1120) there were 5 cases with ulcerative colitis, 2 with Crohn's disease, 1 with SJS, 2 with allergic dermatitis, 2 with a toxic drug reaction, 2 with psoriasis, 1 with DRESS, 2 with angioedema, 1 with a lupus-like syndrome, 1 with leukocytoclastic vasculitis and 1 with autoimmune thyroiditis. In the sponsor's submission, a total of 22 subjects treated with DAC HYP were identified with the adverse events of colitis, ulcerative colitis or Crohn's disease, in contrast to 0 subjects treated with placebo or IFN- β 1a (Section 2.7.4; p. 89). 12/22 cases were considered serious and yet all improved upon discontinuation of DAC HYP, without treatment with a biological agent or anti-TNF. This observed broad range of possible treatment-associated immune and auto-immune mediated injuries across different organs in tandem with autoimmune toxic profiles known to be associated with other anti-T-cell therapies further justifies a careful assessment of the potential of DAC HYP to induce AIH as well as other forms of DILI.

DAC HYP: Effects on T-cell and NK-cell populations

Patients with MS, an idiopathic neurological disease marked by autoimmune injury of myelinated nerve fibers, have a slightly increased risk for some other autoimmune diseases, including thyroid disease, IBD and psoriasis. In addition, MS may be associated with an increased risk for AIH. However, most reported cases of AIH in MS patients appear to have had unmasking of their autoimmune liver diathesis after initiation of

immune altering treatments, as described above. One of a number of plausible overarching mechanisms that could explain the induction or unmasking of autoimmune liver and other organ injuries associated with some effector T-cell targeting treatments for MS is the exaggerated and unintended inhibition of critically important regulatory T-cells which normally have a dampening effect on auto-reactive T cells. Within the T-cell network, auto-reactive lymphocytes are normally held in check by other T cells that suppress their activity and mediate peripheral immunological tolerance. Of concern, some important elements of this regulatory T-cell network appear to be vulnerable to treatments that have been designed for the inhibition or elimination of auto-reactive effector and cytotoxic T cells that damage myelin-sheathed neurons. A key set of regulatory T-cells that suppress auto-immunity express the FOXP3 transcription factor, a protein that is not expressed in most T effector cells. The sponsor has submitted study data suggesting that FOXP3+ regulatory T-cells were diminished by 60% within 8 weeks in study subjects treated with DAC HYP (Summary of Clinical Pharmacology Studies; 2.7.2). The reduction in numbers of these FOXP3+ T-cells is not surprising. It has been found in a number of published studies that there is a substantial subset of these regulatory T cells which express high levels of CD25. These cells reside in lymphoid tissues and expand after stimulation by Il-2 to suppress auto-reactive T cells which are also normally present. After discontinuation of the anti-CD25 monoclonal treatment in MS patient study subjects, recovery of the FOXP3+ regulatory T-cell population in MS patients is gradual and only returns to baseline approximately 20-24 weeks (5-6 months) after the last dose of DAC HYP.

A reduction of FOXP3+ T-cells in vivo would be expected to promote autoimmune injuries. It is notable, however, that the effects of DAC HYP on regulatory T-cells and other immunocytes which normally dampen autoimmune activity are even more complex. In contrast to its inhibitory effect on FOXP3+ T-cells, treatment with DAC HYP leads to an increase of CD56^{bright} NK cells. This population of cells also suppresses autologous T-cells and promotes immune tolerance. Since CD56^{bright} NK cells express CD-122 (the beta subunit of the human Il-2 R) and not CD-25 (the alpha subunit of the Il-2R) this subpopulation expands (rather than contracts) in response to compensatory upregulating growth signals that coincide with DAC-HYP treatment. In the presence of these opposing responses to DAC HYP treatment by effector cells and different subsets of regulatory cells, predicting when daclizumab would promote overall immune tolerance or autoimmune injury of different organs (e.g. the liver) may be difficult, since it would be determined by the unique treatment-response (time-course) profiles of each immune cell-type, as well as their individual recovery time-curves after the discontinuation of treatment. Thus, there may be biologically significant timeline or cumulative exposure-driven differences among different immune cell types in different patients for the pharmacodynamic (PD) effects of DAC HYP to peak or fully reverse. Although some MS patients treated with DAC HYP may achieve a homeostatic balance of suppressor cells and effector cells in favor of immune tolerance during the steady state (or maintenance) phase of long-term treatment, it is important to emphasize that reductions of overall suppressor regulatory cell activity could be especially pronounced at the other phases of the treatment cycle, causing a shift in the balance between tolerance and autoimmunity. Critical times when such a shift may occur include the early treatment

phase of DAC HYP dosaging as well as late phases after treatment has been discontinued. During these periods, different immunocyte activities may change and/or recover towards pre-treatment baseline levels at different rates. In addition, it is conceivable that inter-current systemic inflammatory illnesses such as infection might alter the intricate balance of autoimmune effector cells and suppressor cell populations, in favor of heightened autoimmunity. For this reason, the treatment time-related risk profiles from the initiation of treatment for DILI that characterize many idiosyncratic hepatotoxins (e.g. INH, troglitazone, etc.) may not apply to agents such as DAC HYP that not only target effector and cytotoxic immune cells, but also perturbate regulatory T-cell and NK-cell networks. Because of differences in the long recovery rates (after discontinuation of DAC HYP) among different subpopulations of regulatory cells that maintain immunological ‘homeostasis’, the large gaps of time following DAC HYP discontinuation before autoimmune-mediated liver injury occurred in some of the cases described below may have a mechanistic basis. Questions that were posed in DNP’s Consult Request are separately listed below in italics, each followed by my response.

Question 1

Please evaluate selected cases of DILI in this application, particularly those in which a diagnosis of AIH was made or suspected (list provided in Attachment) and confirm whether or not you think they are related to use of DAC HYP.

Cases of Autoimmune Hepatitis Appended to Question 1.

- 202 909-001 Autoimmune hepatitis (Fatal; Extended narrative provided in Attachment 2.1)*
- 301 624-012 Acute hepatic failure (AIH in the differential diagnosis)*
- 301 670-035 Autoimmune hepatitis (as per consultant hepatologist)*
- 301 670-024 Hepatic enzyme increased. As per the HAC, patient had cholangitis, however he was already responding to corticosteroid treatment before starting antibiotics.(extended narrative in Attachment 2.4)*
- 203 506-011 Autoimmune hepatitis*
- 302 622-103 Autoimmune hepatitis*
- 303 649 009 Autoimmune hepatitis*
- 203 508-012 Autoimmune hepatitis*
- 202 765-003 Chronic hepatitis (as per HAC patient had underlying Autoimmune Hepatitis)*

Response:

A critical appraisal of individual cases suspected of being causally linked to DAC HYP exposure is a fundamental component in my consult to DNP. The consult has an implied objective to characterize DILI risk causally associated with this product, as well as to determine what opportunities and/or limitations for DILI risk management must be considered if it is marketed in the US. As identified both by the sponsor’s expert Hepatic Advisory Committee (HAC; (b) (4)) and the DNP Clinical Review team, there are a number of clinically significant cases of liver injury that occurred in study subjects treated with daclizumab in the DAC HYP

development program for the treatment of relapsing MS, some of which were found to have phenotypic features of AIH. It is notable that in some of these cases serum autoantibodies that are characteristically present in idiopathic AIH (such as ANA) were not detected.

The major studies in the clinical development program in which the liver injury cases occurred were tabulated by sponsor and are shown in Table 1, below.

Table 1. Daclizumab (DAC) HYP Clinical Studies in Patients with Relapsing-Remitting Multiple Sclerosis (RRMS)

Study No.	Study Description	Number in the Safety Population			Objective
		Placebo	DAC HYP	IFN β -1a	
Placebo-controlled Study					
205MS201	Double-blind, placebo-controlled, dose- ranging study in RRMS subjects DAC HYP SC 150 mg, 300 mg or Placebo 1 dose every 4 weeks for 52 weeks	204	417	--	Evaluation of the safety and efficacy
Active-controlled Study					
205MS301	Double-blind, parallel group, active-controlled study in RRMS subjects DAC HYP 150 mg SC once every 4 weeks for 96 to 144 weeks IFN β -1a IM once weekly for 96 to 144 weeks	--	919	922	Evaluation of the safety and efficacy
Dose-blinded Study					
205MS202	Double-blind extension study of 205MS201 Placebo subjects in 205MS201 were assigned to either DAC HYP 150 mg or DAC HYP 300 mg SC once every 4 weeks for 52 weeks DAC HYP subjects in 205MS201 were assigned to either continue at their current dose of DAC HYP (150 mg or 300 mg) or to receive 5 doses of placebo during a washout period followed by 8 DAC HYP doses (150 mg or 300 mg)	--	517/ (170 new exposures)	--	Evaluation of the efficacy safety and immunogenicity of extended treatment with DAC HYP
Uncontrolled Studies					
205MS203	Single-arm, open-label study of 205MS202 extension study 150 mg DAC HYP SC every 4 weeks in subjects who completed treatment in 205MS202 for up to approximately 6.5 years	--	410 (no new exposures)	--	Evaluation of long-term safety and efficacy

205MS302	Single-arm, open-label study DAC HYP injections using the PFS every 4 weeks over an initial 24-week treatment period (for a total of 6 doses), followed by a 20-week washout period. After completion of the washout period, eligible subjects had the option to resume monthly open-label treatment with DAC HYP 150 mg for up to 3 years (or subjects could elect to complete the study through Week 44 only).	--	133 (n=113 in the main study)	--	Evaluation of the immunogenicity of DAC HYP using a pre-filled syringe
205MS303	Single-arm, open-label extension study of 205MS301 DAC HYP 150 mg SC once every 4 weeks for 33 mean cumulative doses	--	308 (146 new exposures)	--	Evaluation of long-term safety and efficacy
Total					
Subjects in the Safety Population for DAC HYP MS Studies		204	2004	922	--

DAC HYP Study Subjects: Graphic Displays of Peak ALT vs Bilirubin

The presence of a clinically significant hepatotoxic potential of DAC HYP is consistent with the finding of higher percentages of randomized study subjects with liver injury in the DAC HYP treatment arm vs subjects who received placebo (Study 201) or the comparator agent (IFN- β 1a; Study 301). Concern that DAC HYP is associated with a relatively high risk of DILI and drug-induced AIH in MS patients has been fueled in Study 301 by the presence of a substantially larger percentage of clinically significant liver injuries in patients randomized to receive the monoclonal antibody compared to IFN- β 1a (even though this comparator agent has been implicated in a number of previously published case reports of severe DILI in MS patients). These differences in the rates of liver abnormalities are highlighted in the 2-dimensional graphic displays of the treatment populations plotting peak serum ALT (fold upper limit of the reference range; ULRR) vs peak total bilirubin (ULRR) [Figures 1 and 2; see below; kindly provided by Dr. Villalba Lourdes, DNP Medical Officer, in a JReview format]. It is important to note that many (but not all) of the individual liver injury cases, upon careful evaluation appear to be etiologically related to causes other than DAC HYP exposure, and thus would be excluded once a case-level review is performed.

Study subjects who developed abnormal serum liver tests that may be of interest appear in both the RUQ and RLQ. Lists of these subjects corresponding to the numbered subjects in each of the graphs appear under Figures 1 and 2.

The review of potential cases of DILI associated with DAC HYP treatment includes 1) cases which are consistent with AIH that are listed in the attachment to the consult request (see above), 2) cases of interest identified above in Figures 1 and 2, and 3) other cases. In response to an Information Request from FDA issued on 9/15/15 that I sought, the sponsor has provided comprehensive case descriptions incorporating all available

clinical and diagnostic test information that has been organized in a treatment time-course format (See Appendix). My assessment of each case regards clinical phenotype, severity and causal association with DAC HYP is discussed below. In conformity with a widely applied method for expert adjudication of potential DILI cases in clinical trials that has been adopted by FDA reviewers, the NIH DILIN network, and many academic experts and industry stakeholders in the US (including the HAC used by the sponsor) I assessed the clinical and biochemical liver injury phenotype of each case of interest. I also used a 5-level scale of clinical severity of new onset liver injury and a comprehensive assessment of differential diagnosis to establish one of 5 levels of causal association with DAC HYP (See Appendix).

Figure 1. Study 201 treatment population; Peak Serum ALT vs Bilirubin

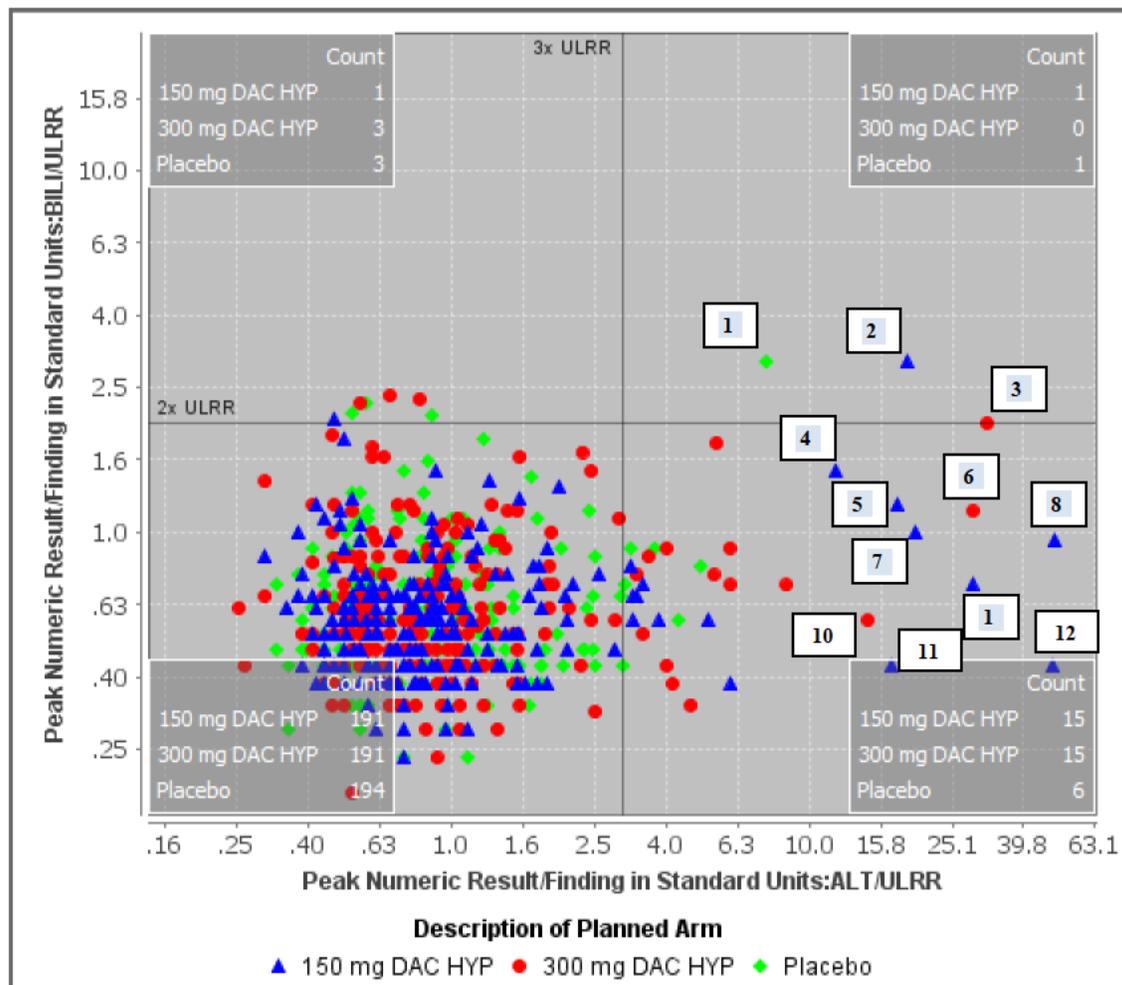
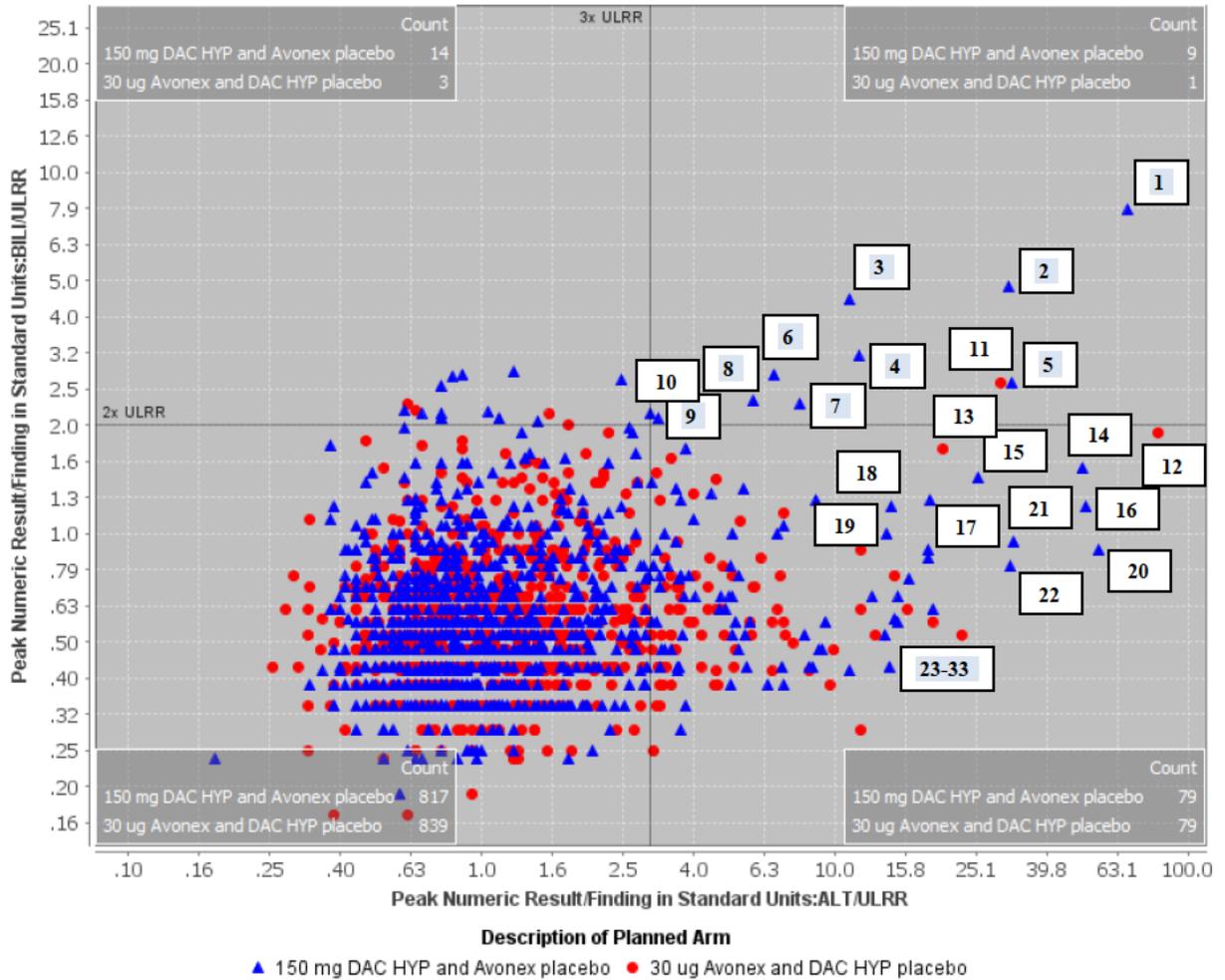


Figure 2. Study 301 treatment population; Peak Serum ALT vs Bilirubin

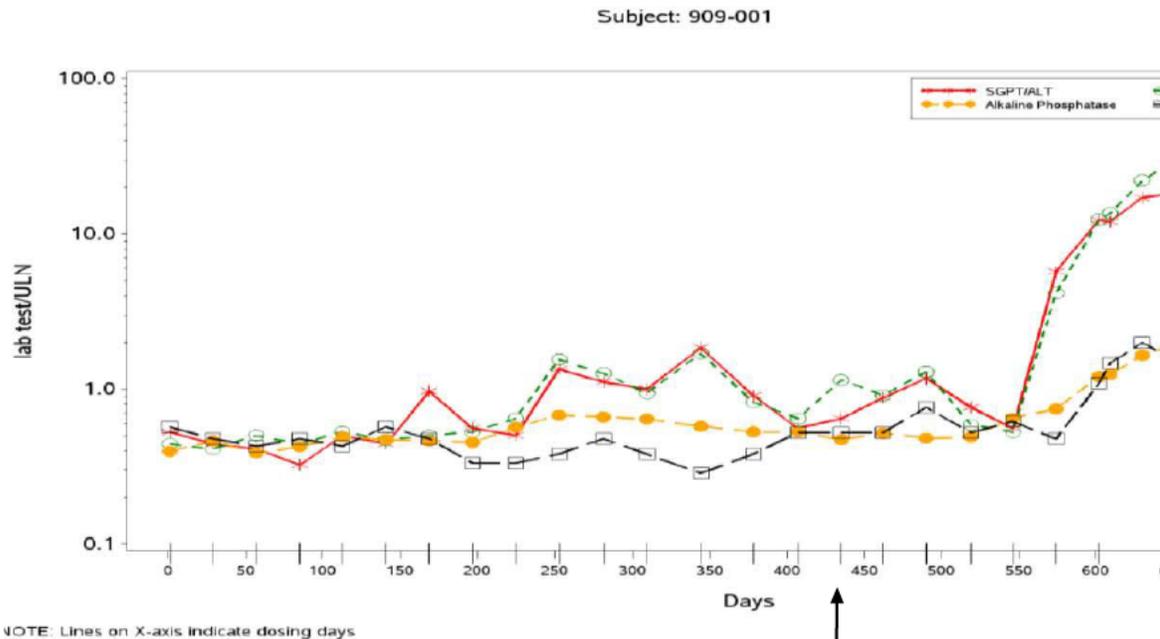


Assessment of Cases of ‘Autoimmune Hepatitis’ Identified by the Sponsor & DNP

Case 202 909-001 (Fulminant Liver Failure)

This case of serious liver injury in a 45 yo WF with an outcome of death due to fulminant hepatitis with liver and multi-organ failure was extensively reviewed and highlighted by the sponsor’s HAC as being ‘Probable’ in causal association with DAC HYP. A full account of the case developed by the HAC (the clinical and biochemical time course, as well as comprehensive diagnostic information and post-mortem pathological analysis) has been provided by the sponsor. In this case, after one year of continuous treatment with DAC HYP there was no evidence of clinically significant liver disease. After a 5-month washout period, the patient developed a relapse of MS and was given a 3-day course of high dose IV methylprednisolone. At that time, monthly dosing of DAC HYP was also resumed, with no evidence of liver injury. Approximately 2 months later, at the

time of administration of the 3rd dose of DAC HYP after the washout period, lab tests revealed new increases of serum ALT (195 U/L) and AST (141 U/L) with normal ALP and bilirubin levels. Over the next two months the patient received 4th and 5th monthly doses. During this period the serum aminotransferase levels continued to rise and the bilirubin level rose slightly above the ULN. Even though treatment with DAC HYP was discontinued, the liver indicators steadily worsened with the advent of frank jaundice within the next two months and the development of fulminant liver failure. The biochemical course is shown in the following figure prepared by the HAC.



Source: HAC Report (pg 24)

First dose of DAC 300 mg after the placebo washout

Upon hospitalization, a full diagnostic workup excluded viral infections and obstructive cholangiopathies, and a clinical diagnosis of autoimmune hepatitis was made. Even though an auto-antibody screen was negative serum Igs were globally elevated with increases of IgE, IgA, IgG and IgM, two days before the patient died. Although the serological autoimmune antibody marker testing for ASMA, SLA, LKM and ANCA was uniformly negative, the histopathological report at necropsy identified extensive plasma cell, leukocytic and lymphohistocytic infiltrates, together with ballooning degeneration, active necrosis, organ hemorrhages and evidence of hepatocellular regeneration (These features are evident in the digitalized images that were submitted to FDA by the sponsor on 9/28/15 in response to an information request). All of these findings are consistent with aggressive AIH. Of note, negative serological testing only characterizes $\leq 7\%$ of cases of acute idiopathic AIH. On the other hand, this finding together with the clinical and biochemical course and histopathological findings have typified many of the cases of autoimmune DILI causally linked to a number of T-cell targeting treatments, including ipilimumab and IFN- β 1a (see above). Based on the temporality of these events, the

absence of an underlying history of idiopathic AIH and the negative autoantibody screen, the conclusion by the HAC that the acute liver injury is 'Probable' in its causal association with DAC HYP is correct in my view.

Case 301 624-012 (#1, Figure 2)

This case of a 35 yo WF developed acute liver failure after receiving 7 consecutive monthly doses of DAC HYP. The event was marked by very high serum aminotransferases (ALT ~ 34X ULN), elevated GGT (4.1X ULN), hyperbilirubinemia (total bilirubin ~ 7.7X ULN) accompanied by clinical jaundice and an increased INR (1.8). The patient had also been treated with valproic acid for 9 weeks leading up to the event as well as had taken Herbalife in that time frame. Carbamazepine which was used for 2 weeks had been discontinued 9 weeks earlier. Upon hospitalization due to the acute liver injury, both DAC HYP and valproic acid were discontinued. A comprehensive assessment for non-drug etiologies was negative and after a brief phase of further the deterioration the patient recovered. A liver biopsy report identified findings of centrilobular and bridging necrosis accompanied by hepatocellular regeneration – findings consistent with DILI. It is notable that liver biopsy findings, as well as serum gamma globulins and serological testing and did not show evidence of AIH. Although valproic acid-induced hepatotoxicity cannot be excluded as a cause, the findings of elevated serum GGT levels and absence of findings of microvesicular steatosis in the liver biopsy report (both characteristic of valproic acid-induced DILI) discounts this possibility. Herbalife-induced liver toxicity is not ruled out, but the time frame and levels of exposure to this product were poorly documented. The HAC concluded that the liver injury is 'Probable' its causal association with DAC HYP. Taking into account the concomitant exposures to the other two agents as well as the findings described above, cogent arguments could be made that the likelihood of association is either 'Probable' or 'Possible'.

Case 301 670-035 (#15, Figure 2)

This 29 yo WM with no known hx of pre-existing liver disease and a normal pre-treatment screen of serum liver tests received 17 doses of DAC HYP. The treatment was discontinued on Day 447 with the advent of robust acute rises of serum ALT (16X ULN) and AST (7X ULN) while the serum bilirubin remained normal. Despite discontinuation the aminotransferase levels remained elevated and were accompanied by the presence of low titers of IgG directed against Hepatitis E and EBV (consistent with previous resolved infections), as well as some liver cellular antigens. Hepatitis B and C serological testing as well as serum autoantibodies were negative; imaging of the abdomen with US was unrevealing. With further increasing levels of ALT/AST 7 weeks after discontinuation of DAC HYP and a rising total bilirubin (1.14X ULN), a liver biopsy was performed which was reported to show hepatitis with lymphocytic infiltration, necrosis and mild fibrosis in the portal areas. Over the next 5 months the ALT/AST levels remained elevated but trended towards normal; however they did not normalize and intermittently worsened with flares towards the end of this period. With no resolution 7 months after discontinuation of DAC HYP and the spontaneous development of an increase of necro-inflammatory activity (ALT 7X ULN), po prednisolone with tapered dosaging was started. Although there was little improvement for the first 6 weeks of prednisolone

treatment, the liver indicators subsequently improved. 14 weeks after prednisolone was initiated, the serum aminotransferase test abnormalities all resolved (it should be noted that serum total bilirubin levels have hovered at times just above the ULN, without fractionation data). These findings are consistent with loss of normal regulatory modulation of immunocytes leading to an autoimmune liver injury after continuous treatment with DAC HYP for 14 months. Given 1) an absence of liver disease prior to treatment with DAC HYP, 2) the prolonged course until resolution of liver injury, 3) the diagnostic exclusion of subacute and chronic types of viral hepatitis and cholangiopathic diseases, and 4) the absence of autoantibodies that are typically present in idiopathic AIH, a causal association of the liver injury with the monoclonal agent is 'Probable' in my view. Nonetheless, further clarification of the patient course after cessation of prednisolone should be obtained from the sponsor.

Case 301 670-024 (#2, Figure 2)

This case of a 33 WM with acute cholestatic liver injury marked by sudden onset of high bilirubin, ALT/AST and ALP levels 11 weeks after DAC HYP treatment was completed was found on MRI cholangiopancreatography to have mild segmental narrowing of the intrahepatic bile ducts, and mild enlargement of a hepatic hilar lymph node. Consistent with the HAC's appraisal, his improvement after treatment with antibiotics suggests a likely diagnosis of cholangitis, and renders a causal link of the liver injury with DAC-HYP as 'Unlikely', in my assessment.

Case 203 506-011

In this case a 34 WF developed liver injury after receiving 49 doses of DAC HYP over the course of 2 consecutive studies. The event was marked by acute rises of ALT and AST which precipitated hospitalization on Day 656 of treatment in study MS203 with peak values on Day 674 of ALT (22X ULN), AST (13X ULN) and bilirubin (1.38X ULN). Further workup revealed a negative screen for ANA, ASMA and AMA, as well as viral hepatitis B and C. With these findings she was started on an oral prednisone taper 10 days later. 3 months later her liver test abnormalities resolved at which time the prednisone dose had been tapered to 5 mg/day. No further lab abnormalities were noted on subsequent visits. The investigator interpreted this to be a case of AIH. Because of the absence of evidence of preexisting liver disease, normal liver tests during the earlier phases of treatment lasting close to 2 years, the negative screen for ANA and gradual resolution with prednisone treatment, the causal association with DAC HYP exposure is 'Probable' in my assessment.

Case 302 622-103

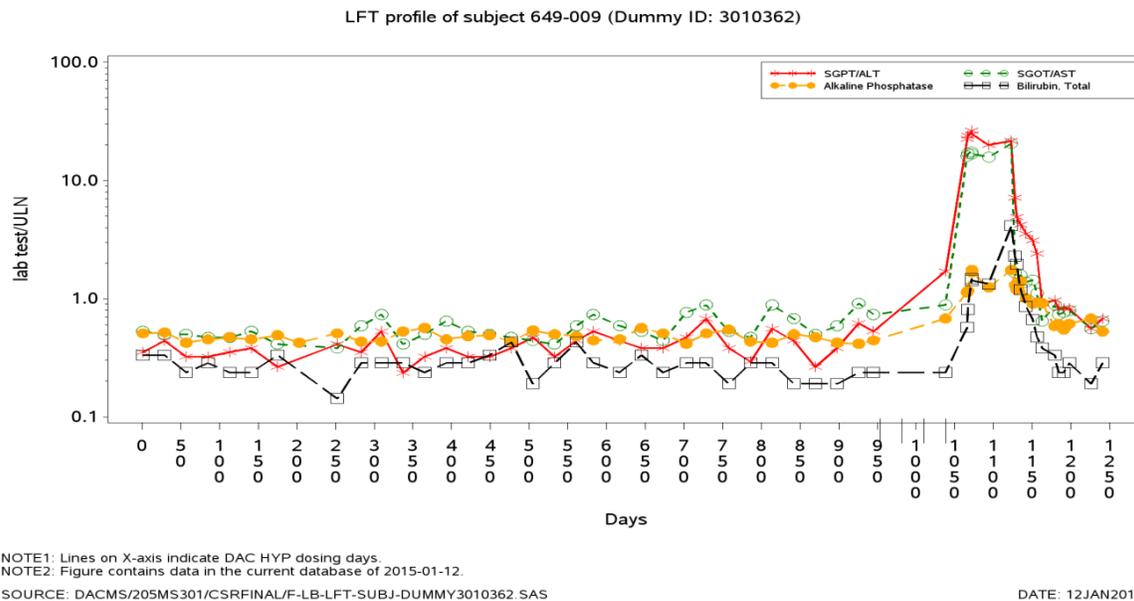
This case of a 42 yo WF was marked by an acute onset liver injury occurring after 5 monthly doses of DAC HYP after which the treatment was permanently discontinued. Pre-treatment liver tests as well as during the earlier phase of the treatment were WNL. Longstanding concomitant medications included lamotrigine, amantadine and tolperisone. 3 weeks prior to the liver injury event leading to DAC HYP discontinuation the patient was given a 3-day pulse treatment of IV methylprednisolone for an MS flare. A diagnostic workup for viral hepatitis was negative. Despite gradual improvement, with ongoing abnormalities of liver tests, over the next 7 weeks tolperisone and lamotrigine

were discontinued. Approximately 11 weeks after DAC HYP discontinuation the liver tests were virtually WNL. At that time, another MS relapse prompted another pulse treatment with IV methylprednisolone. 3 weeks later the ALT and AST levels rose to 4.29X ULN and 3.82X ULN, respectively. With rising levels of ALT and AST to 13X ULN and 16X ULN, respectively as well as increased bilirubin levels to approximately 2X ULN marked by increases of the direct fraction, 3 weeks later the patient was hospitalized for diagnostic tests. A liver biopsy demonstrated diffuse chronic hepatitis, portal fibrosis and lymphocytic infiltrates. With ongoing liver test abnormalities and a clinical impression of findings consistent with AIH the patient was started on oral azathioprine and prednisone. Within a short period the liver test abnormalities resolved. It appears that the liver test abnormalities started during treatment with DAC HYP. The ongoing subsequent fluctuations with flares after IV methylprednisolone pulses suggest contribution of injury by this protocol, an idiosyncratic type of reaction that has been documented in the literature. However, the findings of the liver biopsy and a continuation of elevations of ALT and AST until immunosuppressive treatment was initiated is consistent with an ongoing process autoimmune liver injury. Given the negative test results of ANA or other serological markers that are characteristic of idiopathic AIH, it is plausible that the process was triggered by DAC HYP treatment. However, because of the complexities in this case, I agree with the HAC assessment that this case that the association of DAC HYP with the liver injury is 'Possible' but not 'Probable'.

Case 303 649 009

This 46 yo WF with no known history of preexisting liver disease was enrolled in Study MS301 and received a course of weekly IFN β -1a for a period of at least 96 weeks. With no abnormalities of liver tests, she was then entered into Study MS303 and received 4 monthly doses of DAC HYP (150 mg SC). At the time of the 4th dose of DAC HYP she was noted to have serum elevations of ALT (1.71X ULN), and subsequent treatment with the monoclonal agent was discontinued. 4 weeks later the ALT and AST dramatically rose to 25X ULN and 17X ULN, respectively with an ALP level of only 1.17X ULN. At that time the bilirubin had risen to 1.48X ULN. The time course of serum liver tests prepared by the HAC is shown below. On diagnostic testing screening of hepatitis viral serology was negative, but serum ANA was detected in a significantly high titer (1:160), showing a homogenous pattern on IF; anti-SMA was also positive (1:20). These findings, in conjunction with raised IgG levels (18.9 gm/L), point to a diagnosis of new onset AIH. 10 weeks after discontinuation of DAC HYP the patient was hospitalized with fatigue and jaundices. Ultrasound imaging of the abdomen was consistent with chronic gallbladder changes and chronic pancreatitis. Biochemical testing revealed dramatically raised liver test indicators: ALT 27X ULN, AST 37X ULN, ALP 1.7X ULN and total bilirubin 8.7 mg/dl with a direct fraction of 5.78 mg/dl; the PT was elevated (21 seconds, UNL ~ 18 seconds). These findings reflect the acute onset of severe hepatocellular toxicity (in this case driven by autoimmune hepatitis) and are consistent with Hy's law, if causally connected to a pharmaceutical exposure. IV methylprednisolone was started and then switched to a tapering po dose regimen of the corticosteroid. The patient improved rapidly and 9 weeks later had normal liver tests. Although methylprednisolone was discontinued at that time, due to the appearance of

thrombocytopenia 10 days later, the patient was given a second course of steroids that was then tapered successfully.



With the absence of liver abnormalities prior to treatment with DAC HYP and the extensive diagnostic workup that ensued, my assessment of causal association of DAC HYP with the initiation, exacerbation or unmasking of autoimmune-driven liver injury is ‘Probable’. It should be emphasized that this case raises important concerns about the safety of DAC HYP in certain vulnerable MS patients. Such individuals include those with an increased susceptibility due to preexisting quiescent idiopathic AIH or with a related active or latent autoimmune diathesis (involving the liver as well as other organs) that is prone to being aggravated or unmasked by DAC HYP-induced shifts of regulatory immunocytes towards a state of heightened autoimmunity. DAC HYP treatment should probably be avoided in MS patients with these characteristics until more is known scientifically about the detailed mechanisms that underlie the monoclonal associated liver injury.

Case 203 508-012

This 39 yo WF with no history of preexisting liver disease and normal liver test results during screening received 13 monthly doses of DAC HYP (300 mg) in Study MS202, followed by 49 doses of DAC HYP (150 mg) in Study MS 203. During this period her liver test results remained normal. Treatment was discontinued when she was noted to have developed elevations of ALT (8.3X ULN) and AST (5X ULN) with normal ALP and Bilirubin levels. [6 weeks earlier she had received a 5-day pulse treatment of high-dose IV methylprednisolone for MS relapse.] The screening of viral hepatitis serology and an auto-antibody screen (including ANA, anti-SMA and AMA) was uniformly negative. Over a period of 7 weeks after discontinuation of DAC HYP the patient’s liver aminotransferase enzymes remained elevated and a liver biopsy was performed. It revealed pericentral necrosis of hepatocytes with lymphoid cell infiltrates and eosinophils, consistent with DILI. She was given a clinical diagnosis of autoimmune

hepatitis that according to the investigator was ‘related’ to the study treatment and was started on tapering doses of po prednisone. One month later, after assessment by a hepatologist, the prednisone dose was raised to 60 mg daily and azathioprine was added to her regimen, resulting in a significant decrease in her aminotransferase levels. After 3 months the liver test results were normalized and she continued tapering the dose of prednisone. After another 3 months her prednisone dose had been reduced to 15 mg daily and her clinical status was improved. It should be emphasized that although the serum bilirubin levels did not rise, after it was triggered, the liver injury was protracted and has posed a significant clinical risk to the patient. In particular, the clinical decision to treat the patient over many months with supra-physiological doses of systemic corticosteroids in conjunction with azathioprine to suppress DAC HYP associated liver injury is in of itself connected to a series of known clinically significant short-term and long-term risks. This case is consistent in its lab signature (including a negative ANA screen) as well as its long latency from the beginning of DAC HYP treatment to the initiation of autoimmune liver injury with other cases in the development program. I agree with the Study Investigator that in the absence of an alternative etiology and in the face of negative ANA testing, the autoimmune liver injury is ‘related’ to DAC HYP exposure. In my view, a causal association of auto-immune mediated hepatotoxicity with this agent is ‘Probable’.

Case 202 765-003

This 28 yo WF received a total of 25 monthly doses of DAC HYP 300 mg while sequentially enrolled in MS201 and MS 202. Although the patient’s pretreatment serum ALT and AST levels were normal, her baseline total bilirubin levels were mildly elevated without the benefit of diagnostic fractionation to measure proportions of the conjugated and unconjugated forms. The patient developed increased levels by 14 weeks after the initiation of treatment (5.5X ULN and 3X ULN, respectively) in conjunction with a mildly elevated ALP and total bilirubin levels (between 1 and 2X ULN). A viral hepatitis screen was negative; ANA was slightly positive (1:40) with a speckled pattern on IF. Within a few months she was diagnosed with frank thyrotoxicosis and a toxic goiter which was not adequately suppressed pharmacologically (the patient continued to manifest high levels of free T4, and low TSH levels). Although she was also diagnosed with chronic hepatitis with liver test abnormalities which resolved approximately 5 months after discontinuation of DAC HYP, details surrounding this case do not support DAC HYP-associated liver injury. It is more likely that the findings reflect alterations induced by Gilbert’s Syndrome (reflected by the high pre-treatment bilirubin levels) and thyrotoxicosis (development of the elevations of serum ALP and ALT). I agree with the HAC that the causal association of liver abnormalities in this case with DAC HYP is ‘Unlikely’. It may be of interest to consider whether DAC HYP has an effect on the risk for unmasking or aggravating Grave’s disease or other thyroid autoimmune conditions.

Assessment of Other Selected Liver Injury Cases of Interest

In conjunction with cases described in the preceding section, Figures 1 and 2 show other individuals in the treatment populations of Studies 201 and 301 who developed significant peak liver test abnormalities (indicated in the legends of these figures shown

above by numeral identifiers). Although non-treatment etiologies were identified in the diagnostic workups of some of these individuals, assessment of some of the cases was hampered by insufficiency of clinical and diagnostic information that has been provided by the sponsor. Nonetheless, a number of acute liver injury cases remain which are plausibly causally associated with DAC HYP. I have selected a few of these cases of interest for assessment in this section. In Study 201 (Figure 1), I examined cases with ALT \geq 3X ULN together with Bilirubin \geq 2X ULN [Right Upper Quadrant (RUQ)] and cases in the Right Lower Quadrant (RLQ) with ALT \geq 10X ULN. In Study 301 (Figure 2) I examined all cases in the RUQ and cases in the RLQ with ALT \geq 15X ULN.

Study 201 (Figure 1)

Case 908-005 (#10)

This 37 yo WF received 64 monthly doses of DAC HYP (Studies MS201, MS202 and MS203) only interrupted during a 5 month period between the 13th and 14th dose. At the end of the 13th dose (Day 363) the patient developed elevations of serum ALT and AST (14.6X ULN and 7.7X ULN) which resolved one month later while DAC HYP was held. Diagnostic tests for Type B and C viral hepatitis were negative. During the second treatment phase with DAC HYP, after 4.5 years the patient developed a second episode of elevated aminotransferases with the ALT and AST peaking at 19.5X ULN and 11.9X ULN, respectively. The serum bilirubin levels remained normal during both episodes. With no history of pre-existing liver disease and absence of a defined alternative diagnosis, the investigator concluded that both events were related to the study treatment and the patient was withdrawn from the study. Although the clinical report does not provide any information about whether other diagnostic studies such as hepatobiliary imaging were performed, with the temporal characteristics that have been described and the clinical course signatures that characterize other cases in the development program it is plausible that the liver injuries are causally associated with DAC HYP. In my view this causal association could be interpreted as ‘Possible’ or ‘Probable’.

Case 763-011 (#11)

This 35 yo WM received 12 monthly doses of DAC HYP when he developed acute elevations of ALT and AST that peaked at 17X ULN and 9X ULN, respectively. Both the ALP and Bilirubin levels remained normal. These abnormalities quickly resolved upon discontinuation of DAC HYP. In the face of no preexisting liver disease, an unremarkable physical exam related to these findings in conjunction with a negative screen for Hepatitis B and C, the investigator assessed the liver injury as ‘related’ to the study treatment. I concur with that conclusion and would assess the causal association of the liver injury with DAC HYP as ‘Possible’ or ‘Probable’.

Study 301 (Figure 2)

Case 604-040 (#5)

This 31 yo WM developed acutely elevated levels of serum ALT (32X ULN), AST (22X ULN) and Total/Direct Bilirubin (2.6X ULN/5X ULN) after receiving 14-monthly doses of DAC HYP which was then discontinued. At the time of the event the GGT was 7.9X ULN and the ALP was 1.5X ULN. Concomitant medications included venlafaxine and

carbamazepine which were started and then dose-titrated upwards approximately 9 weeks before the liver injury event. Viral hepatitis serology was negative and an MRCP did not reveal extra-hepatic cholestasis. The HAC concluded that the causal association of this hepatotoxic event with DAC HYP is 'Possible' but that it is more likely that the culprit is carbamazepine. I concur with this conclusion.

Case 205-006 (#14)

This 33 yo WF with MS and a hx of hypothyroidism received 16 monthly doses of DAC HYP before developing mild increases of serum ALT (3.4X ULN) and AST (1.3X ULN) which rapidly resolved after a one-month treatment interruption. There was no history of preexisting liver disease prior to enrollment and screening studies were unremarkable other than the ALT was transiently elevated (50 U/L). Upon reinstatement of treatment, after another 5 months the patient developed much more pronounced rises of ALT (50X ULN), AST (22X ULN) and Total/Direct Bilirubin (1.5X ULN/2.14X ULN) with normal ALP levels, and the DAC HYP treatment was discontinued. An extensive diagnostic workup revealed a significant serum ANA titer (1:80) that is characteristic of AIH. Hepatitis virus serological testing (Hepatitis A, B, C and E) was negative 3 weeks after the acute increases of the liver serum aminotransferase tests; these indicators returned to values similar to those that preceded the acute liver injury, rising at times to levels slightly above the upper limit of normal. For the next 12 months this biochemical picture remained stable. Although the patient was not reported to have been treated with corticosteroids to quell the acute liver injury event, it is plausible that she had underlying AIH which was aggravated because of treatment with DAC HYP. The investigator concluded that the event was 'related' to study drug treatment. In my estimation, the causal association of the liver injury with DAC HYP is 'Possible'. Given that a disease (AIH) – drug (DAC HYP) interaction is plausible and other causes of acute liver injury or AIH exacerbation appear to have been excluded, it could be argued that the causal association with DAC HYP is 'Probable'.

Case 592-001 (#16)

This 44 yo WF with no history of preexisting liver disease and with negative viral hepatitis screening at the time of study enrollment developed acute rises of serum ALT (51X ULN) and AST (20X ULN), with no rise of total bilirubin or ALP, after receiving 13 monthly doses of DAC HYP. The monoclonal antibody as well as concomitant medications (including ketoprofen, pantoprazole and baclofen) were discontinued. Sertraline and zolpidem had been discontinued at least one month before the onset of the liver injury). An extensive diagnostic workup excluded viral hepatitis and idiopathic AIH. The serum test abnormalities almost resolved within 9 weeks after discontinuation of DAC HYP (ALT 2.6X ULN; AST 1.6X ULN) but unexpectedly increased a second time to comparable levels as in the earlier episode, this time accompanied by mild elevations of serum bilirubin (1.46 mg/dL) and GGT (2X ULN). These increases returned to normal levels 3 months later. It should be noted that ketoprofen has been associated with a low rate of substantial increases of serum aminotransaminases, often transient within a few months of initiation of treatment. In this case, ketoprofen had been started more than 7 months before the liver event occurred. The dual peak rises of aminotransferase levels separated by 9 weeks are enigmatic, pointing to the importance

of excluding intermittent use of other hepatotoxic products. The investigator concluded that the liver injury event was ‘related’ to DAC HYP. I agree with that characterization but conclude that the causal association in this case is only ‘Possible’.

Case 453-026 (#17)

This 20 yo WF received 2 monthly doses of DAC HYP when she was found to have acute elevations of ALT (18.6X ULN) and AST (13.7X ULN) with normal ALP and total bilirubin levels. There was no prior history of liver disease and pre-treatment screening for Hepatitis B and C was unremarkable other than the presence of HBV Ab. At the time of the liver injury the patient has also been taking acetaminophen for 2 months (reason and dosing not described) and estrogen/progesterone. Serum tests for viral hepatitis (Types A, B, C and E), other viruses, ANA and ASMA were uniformly negative, other than the presence of anti-CMV IgG and anti-HSV1 IgG. 12 days later an abdominal US revealed liver steatosis. There is no indication that a liver biopsy was performed. The cause of liver injury was diagnosed by a hepatologist as drug-induced hepatitis and the patient was treated with prednisolone. 12 weeks later the liver test abnormalities had all resolved to baseline pretreatment levels. It is notable that in this case the onset of liver injury was relatively shorter than in other cases in this series. I agree with the investigator’s assessment that the liver injury is ‘related’ to DAC HYP. Given the relatively short period between initiation of the monoclonal antibody treatment and the liver injury (2 months) compared to other cases in this series, and with little information provided regards acetaminophen exposure, in my judgment the causal association of this event with DAC HYP is only ‘Possible’.

Causal Association with DAC HYP that is only ‘Possible’ or ‘Unlikely in Other Assessed Cases with Liver Abnormalities (Studies 201 and 301)

Due to the presence of equally or more likely alternative etiologies that would cause the observed liver abnormalities or an absence of essential clinical or diagnostic information, my assessment of other cases of liver injury in the RUQ as well as cases in the RLQ with ALT >10X ULN (Figure 1) or ALT > 15X ULN (Figure 2) finds a causal association with exposure to the monoclonal antibody that is only ‘Possible’ or ‘Unlikely’ in the following cases:

Study 201 (Figure 1)

- Case 763-005 (#2)***
- Case 110-005 (#4)***
- Case 761-024 (#5)***
- Case 752-018 (#6)***
- Case 460-010 (#7)***
- Case 763-004 (#8)***
- Case 903-025 (#9)***
- Case 509-007 (#12)***

Study 301 (Figure 2)

- Case 517-003 (#3)***

Case 649-006 (#4)
Case 659-019 (#6)
Case 660-007 (#7)
Case 611-007 (#8)
Case 148-004 (#9)
Case 605-002 (#10)

Summary of Case Findings

In the DAC HYP clinical trial development program for MS approximately 2,000 patients were treated with the monoclonal agent. 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 there were substantial titers of these antibodies, suggesting that the agent may also exacerbate or unmask underlying autoimmune diatheses involving the liver.

Question 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?

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.

How to develop a strategy for the identification and risk minimization of DILI depends on the following considerations: 1) the expected number of DAC HYP treated patients and patient-level patterns of use (dosing, duration of use, range of cumulative exposures, etc.), 2) the predicted incidence of clinically serious DAC HYP-induced DILI and the range of susceptibility in the domestic MS treatment population, 3) the range of clinical signature(s) and clinical severity of individual cases of DILI associated with this product (time to onset, speed of injury progression, reversibility of injury upon treatment modification, 4) the healthcare environment (presence/absence of accessible expertise, infrastructure and insurance carrier support to regularly assess patients both clinically and with biochemical monitoring) and 5) the surveillance strategy that is established (system in place to identify, characterize and report DAC HYP associated adverse events, as well as measure its utilization in MS patients) in order to define more fully its risk profile in real-world post-market populations. Since DAC HYP would be intended for long-term administration to treat chronic RRMS and some cases of treatment-induced AIH developed only after a long period on treatment, or as long as 6-12 months after discontinuation of treatment, an optimal risk management plan for DAC HYP-associated DILI would require long-term clinical and biochemical monitoring by healthcare providers in conjunction with a commitment to evaluate and manage therapy for hepatotoxicity in a pro-active manner. Such an effort would be possible only in the context of a healthcare provider network or system with the necessary resources and expertise to care for patients with MS, as well as educate both patients and healthcare providers to effectively recognize and manage adverse reactions associated with DAC HYP.

It is important that patients be instructed about the symptoms and signs of acute hepatitis (new onset fatigue, nausea and vomiting, jaundice, etc.) to seek out medical attention when these occur. 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.

Question 3

Do you believe that the risk of DILI with DAC HYP would be effectively minimized with appropriate labeling, with, or without, a REMS?

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 and diagnostic interventions and appropriate treatment alterations are made in a timely manner if liver injury or other adverse events are detected. In addition, in concert with a warning (or boxed warning) in the product labeling, as well as a MedGuide, it is important to reinforce messages about risks associated with DAC HYP to all patients through an educational program. Such a program would afford an opportunity to adequately instruct patients about the signs and symptoms of liver injury, including the onset of fatigue, nausea, jaundice, dark urine, etc, as a prompt for immediate discontinuation of self-administration of the product and contacting the HCP for evaluation. [This approach of self-monitoring for early signs and symptoms of acute serious DILI as a prompt to immediately discontinue treatment has been employed in a large health care system to reduce the risk for acute liver injury caused by INH. Self-monitoring is likely to be a less effective tool as a preventative measure against smoldering or chronic forms of DILI].

Question 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?

Because reliable information about the long-term treatment effects on safety and efficacy of DAC HYP for MS is critically important to obtain in a post-market setting, a comprehensive approach for HCPs to acquire and report a set of pre-specified data elements for patients with liver injury or other adverse events should be instituted. This 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.

Appendix

I. Sponsor's Response to an Information Request for Narratives of Cases of Interest Issued by FDA on 9/15/15



response-to-narrativ
e-request-dated-15s

II. Assessment of potential drug-induced liver injury of the present cases uses the grading system for likelihood of attribution and liver disease severity developed by the National Institutes of Health's Drug-Induced Liver Injury Network (DILIN) Study Group.*

Likelihood of Causality			
Score	Causality	Likelihood (%)	Textual Definition
1	Definite	≥95	Causality is "beyond a reasonable doubt"
2	Highly Likely	75-94	Causality supported by "clear and convincing evidence"
3	Probable	50-74	Causality supported by the "preponderance of the evidence"
4	Possible	25-49	Less than the preponderance of evidence but still possible
5	Unlikely	<25	Causality unlikely or excluded

Disease Severity Scale		
Score	Grade	Definitions
1	Mild	Elevated ALT and/or Alk P but serum bilirubin <2.5 mg/dL and INR <1.5
2	Moderate	Elevated ALT and/or Alk P and serum bilirubin ≥2.5 mg/dl or INR ≥1.5
3	Moderate- Severe	Elevated ALT and/or Alk P and bilirubin or INR and new or prolonged hospitalization due to dili
4	Severe	Elevated ALT and/or Alk P and serum bilirubin ≥2.5 mg/dl and there is one of the following: -Hepatic failure (INR ≥1.5, ascites or encephalopathy) -Other organ failure (renal/pulmonary) d/t dili
5	Fatal	Death or liver transplant from dili

*Fontana RJ, Seeff LB, Andrade RJ, Bjornson E, DayCP, Serrano J, Hoofnagle HJ. Standardization of nomenclature and causality assessment in drug-induced liver injury: summary of a clinical research workshop. Hepatology 2010;52:73-742

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

/s/

ERMIAS ZERISLASSIE
11/09/2015

MARK I AVIGAN
11/09/2015



Food and Drug Administration
Center for Devices and
Radiological Health
Office of Device Evaluation
White Oak Building 66
10903 New Hampshire Avenue
Silver Spring, MD 20993

Date: July 29, 2015

From: Lana Shiu, M.D.
General Hospital Devices Branch, DAGRID, ODE, CDRH

To: Laurie Kelley/Su-Lin Sun
Division of Neurology Product, Office of New Drugs, CDER

Via: Keith Marin and Ryan McGowan
Combination Products Team Leaders, GHDB, DAGRID, CDRH

Rick Chapman
Branch Chief, General Hospital Devices Branch, DAGRID, ODE, CDRH

Subject: BLA 761029 ZINBRYTA™ (daclizumab High Yield Process) 150 mg/mL Injection
/Applicant: Abbvie
CDRH Tracking: ICC1500104

Indication: for the treatment of multiple sclerosis

Device description

Daclizumab will be marketed in a manual prefilled syringe configuration.

The PFS container closure system consists of a (b) (4)
1 mL long fixed needle syringe (b) (4) utilizing USP/Ph. Eur Type I (b) (4) glass.
Each syringe contains an embedded staked 0.5 inch long, 29 gauge (b) (4),
5 bevel needle for subcutaneous injection, a (b) (4) rubber plunger
stopper, and a rigid needle shield (RNS) (b) (4)
(b) (4) The (b) (4) components (plunger stopper and RNS)
are not made with natural rubber latex (b) (4)
(b) (4)

Table 1: DAC HYP Drug Product Container Closure System

Component	Material	Manufacturer
Container	1 mL Staked Needle Syringe USP Ph.Eur./IP Type I (b)(4) glass 29 Gauge, 0.5 inch long (b)(4) needle	(b)(4)
Closure	Plunger Stopper, Grey (b)(4) rubber stopper (b)(4) (b)(4) grey (b)(4)	(b)(4)
	Compliant with USP and Ph. Eur. Needle Shield (b)(4) Compliant with USP and Ph. Eur.	(b)(4)

Table 2: Specifications for the Syringe Barrel

Attribute	Specification
Description	Sterile, clean, ready-to-fill 1 mL long syringe, 29 gauge, 0.5 inch, 5 bevel needle, with (b)(4) rigid needle shield
Needle (b)(4)	5 bevel
Sterility	Meets current USP <71>, Pharms. Eur. 2.6.1
Bacterial endotoxin	≤ (b)(4) EU/barrel
Type I glass	Conforms
Identification needle shield (b)(4)	Chemical identity rubber (ATR-IR-spectrum)
Syringe length, mm	(b)(4)
Syringe barrel inner diameter, mm	(b)(4)
Syringe barrel inner diameter at the mouth, mm	(b)(4)
Needle shield removal force, N	(b)(4)
Needle pull out force	(b)(4)N
Physical Inspection	Meets minimum AQL requirements

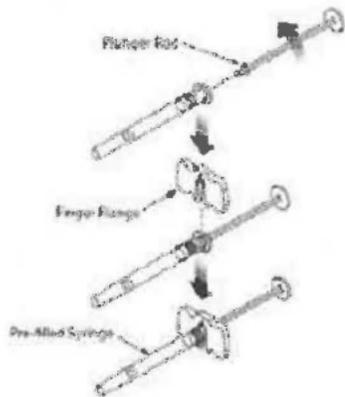
AQL=Acceptable Quality Limits; ATR-IR=Attenuated Total Reflectance Infrared Spectroscopy; EU=Endotoxin Units.

Table 3: Specifications for the Plunger Stopper

Attribute	Specification
Description	Stopper 1 mL (b)(4) grey (b)(4)
Sterility	(b)(4) sterility assurance level
Bacterial Endotoxin	≤ (b)(4) EU/plunger stopper
Identification Rubber	Chemical identity rubber (ATR-IR-spectrum)
Identification Coating	Chemical identity coating (ATR-IR-spectrum)
Plunger Stopper Height, mm	(b)(4)
Plunger Stopper Maximum Outer Diameter, mm	(b)(4)
Plunger Stopper Minimum Outer Diameter, mm	(b)(4)
Physical Inspection	Meets minimum AQL requirements

AQL=Acceptable Quality Limits; ATR-IR=Attenuated Total Reflectance Infrared Spectroscopy; EU=Endotoxin Units.

Component	Description
Finger Flange (Backstop)	1 mL (b)(4) Backstop
Plunger Rod	1 mL (b)(4) Plunger Rod



The staked needle syringes are purchased from the vendor (b) (4) with the rigid needle shield in place. (b) (4)

The plunger stopper is a grey (b) (4). The plunger stopper is currently manufactured by (b) (4) using a (b) (4) formulation and complies with the requirements of the current USP <381> and Ph. Eur. 3.2.9. The plunger stopper is (b) (4)

(b) (4)

List of Standards Applicable to PFS

Document Number	Year Published	Document Title
ISO 10993-1	2009	Biological Evaluation of Medical Devices – Part 1: Evaluation and Testing Within a Risk Management Process
ISO 10993-5	2009	Biological Evaluation of Medical Devices – Part 5: Tests for in vitro cytotoxicity
(b) (4)		
ISO 10993-10	2011	Biological Evaluation of Medical Devices – Part 10: Tests for irritation and skin sensitization
ISO 15223-1	2012	Medical Devices-Symbols to Be Used With Medical Device Labels, Labeling and Information to Be Supplied- Part 1: General Requirements
EN 1041	2008	Information supplied by the manufacturer of medical devices

Document Number	Year Published	Document Title
IEC 62366	2007	Medical Devices – Application of Usability Engineering to Medical Devices
ISO 11040-4	2007	Prefilled Syringes – Part 4: Glass Barrels for injectables
(b) (4)		
ASTM D4169	2009	Standard Practice for Performance Testing of Shipping Containers and Systems.
ISO 14971	2007	Medical devices – Application of Risk Management to Medical Devices.
(b) (4)		
ASTM F1090	2007	Standard Guide for Accelerated Aging of Sterile Barrier Systems for Medical Devices
(b) (4)		

Principle of Operation of the Combination Product

Manual subcutaneous injection via prefilled syringe with staked 29G needle.

Biocompatibility –DMF (b) (4) syringe barrel is glass (inert material) and the needle staked to the syringe (b) (4) which have been reviewed and approved for use previously. Syringe is considered to be external communicating and contact of limited duration per ISO 10993.

Test	Test Method Description	Acceptance Criteria	Test Results
Cytotoxicity	ISO 10993-5: Tests for Cytotoxicity – In vitro methods	Cytotoxicity according to ISO 10993-5 Section 8.5.	Pass
Sensitization	ISO 10993-10: Tests for Sensitization and Irritation	Sensitization according to ISO 10993-10 Section 7.5.6.	Pass
Irritation	ISO 10993-10: Tests for Sensitization and Irritation	Irritation according to ISO 10993-10 Section 7.6.6.	Pass

Sterilization method and validation method as well as packaging

The syringe barrels are packaged (b) (4)
 The syringes meet a sterility assurance (b) (4)
 (b) (4).

The plunger stoppers are then packaged (b) (4)
 (b) (4). The plunger stoppers meet a sterility assurance level (b) (4).



Testing protocols and data -bench,

Syringe Functionality--

A total of 100 syringes (b) (4) from each process consistency validation lot were analyzed (b) (4) for syringe functionality (break loose and glide force). (b) (4)



DP Lot	Sampling Point During Filling	n	Break Loose Force (N)			Glide Force (N)		
			Mean	Standard Deviation	Max	Mean	Standard Deviation	Max
PVR 1 (VVNB16)								(b) (4)
PVR 2 (VVNB17)								(b) (4)
PVR 3 (VVNB21)								(b) (4)
PVR 4 (VVNG92)								(b) (4)
Overall (All 4 Lots)								(b) (4)

Dose Accuracy/Expelled Volume (Acceptance = (b) (4) mL to (b) (4) mL.)

Parameter	Parameter Classification	Action Limit	(b) (4) Specification	PVR1 (VVNB16)	PVR2 (VVNB17)	PVR3 (VVNB21)	PVR4 (VVNG92)	Validation Results
Visual Examination	IPC	According to SOP	NA	Conforms	Conforms	Conforms	Conforms	Pass
Expelled Volume ^a (mL syringe)	CPC	T1 Alert Limit: (b) (4)	T2 Action Limit: (b) (4)					(b) (4)
Plunger Stopper Position ^b	CPC	(b) (4)	NA					

To confirm that the DAC HYP 150 mg/mL formulation would remain compatible with the chosen PFS and not impede the functionality of the syringe with storage, the plunger break loose force, plunger glide force, and needle shield removal force were measured and data are provided for up to 36 months of storage at 2-8°C, up to 6 months of storage at 25°C, and up to 4 months of storage at 40°C. Testing was performed on two drug product lots produced at (b) (4) an engineering run (Lot VVJB08) and a clinical lot (Lot VVLF85). The two lots were manufactured using different (b) (4) PFS lots. Prior to testing, the syringes were equilibrated (b) (4). Testing was performed using an (b) (4). At each time point, a total of 20 syringes were tested for both drug product lots for plunger break loose and glide forces. At each time point, a total of 3 PFS were tested from lot VVJB08 and 20 PFS from lot VVLF85 for needle shield removal force.

Summary of Plunger Break Loose Force, Glide Force, and Needle Shield Removal Force for DAC HYP PFS Lot VVJB08 Stored Through 36 Months at 2-8°C, 5 Months at 25°C, and 3 Months at 40°C (Biogen Idec Testing)

Testing Parameter	Break Loose Force (N), n=20			Glide Force (N), n=20			Needle Shield Removal Force (N), n=3		
	2-8°C (10 to 36 months)	25°C (1 to 5 months)	40°C (1 to 3 months)	2-8°C (10 to 36 months)	25°C (1 to 5 months)	40°C (1 to 3 months)	2-8°C (10 to 36 months)	25°C (10 to 5 months)	40°C (10 to 3 months)
Maximum	(b) (4)								
Average									
Minimum									
Standard Deviation									

Summary of Plunger Break Loose Force, Glide Force, and Needle Shield Removal Force for DAC HYP PFS Lot VVLF85 Stored Through 15 Months at 2-8°C, 6 Months at 25°C, and 4 Months at 4°C (Biogen Idec Testing)

Testing Parameter	Break Loose Force (N), n=20			Glide Force (N), n=20			Needle Shield Removal Force (N), n=20		
	2-8°C (4 to 15 months)	25°C (1 to 6 months)	40°C (1 to 4 months)	2-8°C (4 to 15 months)	25°C (1 to 6 months)	40°C (1 to 4 months)	2-8°C (4 to 15 months)	25°C (1 to 6 months)	40°C (1 to 4 months)
Maximum	(b) (4)								
Average									
Minimum									
Standard Deviation									

For lot VVJB08, through 36 months storage at 2-8°C, the individual plunger break loose force measurements ranged between (b) (4) N; and for lot VVLF85, through 15 months storage at 2-8°C, the individual plunger break loose force measurements ranged between (b) (4) N. No clear trend indicating increase in the plunger break loose force as a function of storage time was apparent for all evaluated temperatures.

Plunger Break Loose Force as a Function of Time and Temperature

For lot VVJB08, through 36 months storage at 2-8°C, the individual plunger glide force measurements ranged from (b) (4)N; and for lot VVLF85, through 15 months storage at 2-8°C, the individual plunger glide force measurements ranged from (b) (4)N. No adverse trend indicating increase in the plunger glide force as a function of storage time was apparent for all evaluated temperatures. Exposure of the product to accelerated and stressed storage conditions during normal shipping and end use conditions is not expected to impact glide force through the proposed commercial PFS expiry period of (b) (4) months at the long-term storage condition of 2-8°C.

Plunger Glide Force as a Function of Time and Temperature

For lot VVJB08, through 36 months storage at 2-8°C, the individual needle shield removal force measurements ranged from (b) (4)N; and for lot VVLF85, through 15 months storage at 2-8°C, the individual needle shield removal force measurements ranged from (b) (4)N. No

clear trend indicating increase in the needle shield removal force as a function of storage time was apparent for evaluated temperatures.

Needle Shield Removal Force as a Function of Time and Temperature

(b) (4)

Plunger break loose force and glide force was also assessed (b) (4) by the PFS drug product manufacturer (b) (4)

(b) (4)

Below is a summary of plunger break loose force and glide force for nine DAC HYP drug product lots manufactured using five unique (b) (4) PFS lots. These data demonstrate consistency of PFS lots with respect to these attributes and are also indicative of the consistency (b) (4) to the syringe lots (performed by the PFS supplier (b) (4)). The glide force results are consistent with the results obtained by Biogen Idec; however, the break loose force results differ slightly due to the difference in test parameters used by (b) (4) compared to Biogen Idec. Specifically, the difference is in identifying the break loose force (b) (4)

(b) (4)

CDRH/ODE/GHDB Recommendation: The sponsor has addressed all of the PFS device-related issues and no further deficiencies are noted.

Digital Signature Concurrence Table	
Reviewer Sign-Off	Lana Shiu, M.D.  Digitally signed by Lana L. Shiu - S Date: 2015.07.29 14:38:15 -04'00'
Branch Chief Sign-Off	 Richard C. Chapman -S 2015.07.29 14:41:00 -04'00'

RPM FILING REVIEW

(Including Memo of Filing Meeting)

To be completed for all new NDAs, BLAs, and Efficacy Supplements [except SE8 (labeling change with clinical data) and SE9 (manufacturing change with clinical data)]

Application Information		
NDA # BLA# 761029	NDA Supplement #: S- BLA Supplement #: S-	Efficacy Supplement Category: <input type="checkbox"/> New Indication (SE1) <input type="checkbox"/> New Dosing Regimen (SE2) <input type="checkbox"/> New Route Of Administration (SE3) <input type="checkbox"/> Comparative Efficacy Claim (SE4) <input type="checkbox"/> New Patient Population (SE5) <input type="checkbox"/> Rx To OTC Switch (SE6) <input type="checkbox"/> Accelerated Approval Confirmatory Study (SE7) <input type="checkbox"/> Animal Rule Confirmatory Study (SE7) <input type="checkbox"/> Labeling Change With Clinical Data (SE8) <input type="checkbox"/> Manufacturing Change With Clinical Data (SE9) <input type="checkbox"/> Pediatric
Proprietary Name: ZINBRYTA™ Established/Proper Name: daclizumab Dosage Form: injection Strengths: 150mg/mL		
Applicant: AbbVie Inc. Agent for Applicant (if applicable): Matthew Kuntz		
Date of Application: 2/27/15 Date of Receipt: 2/27/15 Date clock started after UN: n/a		
PDUFA/BsUFA Goal Date: 2/28/16		Action Goal Date (if different): 12/30/15
Filing Date: 4/28/15		Date of Filing Meeting: 4/6/15
Chemical Classification (original NDAs only) : <input type="checkbox"/> Type 1- New Molecular Entity (NME); NME and New Combination <input type="checkbox"/> Type 2- New Active Ingredient; New Active Ingredient and New Dosage Form; New Active Ingredient and New Combination <input type="checkbox"/> Type 3- New Dosage Form; New Dosage Form and New Combination <input type="checkbox"/> Type 4- New Combination <input type="checkbox"/> Type 5- New Formulation or New Manufacturer <input type="checkbox"/> Type 7- Drug Already Marketed without Approved NDA <input type="checkbox"/> Type 8- Partial Rx to OTC Switch		
Proposed indication(s)/Proposed change(s): treatment of patients with relapsing forms of multiple sclerosis		
Type of Original NDA: AND (if applicable) Type of NDA Supplement:		<input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2) <input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2)
<i>If 505(b)(2): Draft the "505(b)(2) Assessment" review found at:</i> http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027499		

Type of BLA	<input checked="" type="checkbox"/> 351(a) <input type="checkbox"/> 351(k)
If 351(k), notify the OND Therapeutic Biologics and Biosimilars Team	
Review Classification:	<input checked="" type="checkbox"/> Standard <input type="checkbox"/> Priority
<p>The application will be a priority review if:</p> <ul style="list-style-type: none"> • <i>A complete response to a pediatric Written Request (WR) was included (a partial response to a WR that is sufficient to change the labeling should also be a priority review – check with DPMH)</i> • <i>The product is a Qualified Infectious Disease Product (QIDP)</i> • <i>A Tropical Disease Priority Review Voucher was submitted</i> • <i>A Pediatric Rare Disease Priority Review Voucher was submitted</i> 	
Resubmission after withdrawal? <input type="checkbox"/>	Resubmission after refuse to file? <input type="checkbox"/>
Part 3 Combination Product? <input checked="" type="checkbox"/>	<input type="checkbox"/> Convenience kit/Co-package <input type="checkbox"/> Pre-filled drug delivery device/system (syringe, patch, etc.) <input checked="" type="checkbox"/> Pre-filled biologic delivery device/system (syringe, patch, etc.) <input type="checkbox"/> Device coated/impregnated/combined with drug <input type="checkbox"/> Device coated/impregnated/combined with biologic <input type="checkbox"/> Separate products requiring cross-labeling <input type="checkbox"/> Drug/Biologic <input type="checkbox"/> Possible combination based on cross-labeling of separate products <input type="checkbox"/> Other (drug/device/biological product)
<p>If yes, contact the Office of Combination Products (OCP) and copy them on all Inter-Center consults</p>	

<input type="checkbox"/> Fast Track Designation <input type="checkbox"/> Breakthrough Therapy Designation <i>(set the submission property in DARRTS and notify the CDER Breakthrough Therapy Program Manager)</i> <input type="checkbox"/> Rolling Review <input type="checkbox"/> Orphan Designation <input type="checkbox"/> Rx-to-OTC switch, Full <input type="checkbox"/> Rx-to-OTC switch, Partial <input type="checkbox"/> Direct-to-OTC Other:	<input type="checkbox"/> PMC response <input type="checkbox"/> PMR response: <input type="checkbox"/> FDAAA [505(o)] <input type="checkbox"/> PREA deferred pediatric studies (FDCA Section 505B) <input type="checkbox"/> Accelerated approval confirmatory studies (21 CFR 314.510/21 CFR 601.41) <input type="checkbox"/> Animal rule postmarketing studies to verify clinical benefit and safety (21 CFR 314.610/21 CFR 601.42)
--	--

Collaborative Review Division (if OTC product): n/a

List referenced IND Number(s): 012120

Goal Dates/Product Names/Classification Properties	YES	NO	NA	Comment
PDUFA/BsUFA and Action Goal dates correct in tracking system? <i>If no, ask the document room staff to correct them immediately. These are the dates used for calculating inspection dates.</i>	<input type="checkbox"/>	<input checked="" type="checkbox"/>		3/26/15 emailed doc room staff for change to "standard review, NME, the Program for PUDFA V" goal clock
Are the established/proper and applicant names correct in tracking system? <i>If no, ask the document room staff to make the corrections. Also,</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>		

<i>ask the document room staff to add the established/proper name to the supporting IND(s) if not already entered into tracking system.</i>				
Is the review priority (S or P) and all appropriate classifications/properties entered into tracking system (e.g., chemical classification, combination product classification, orphan drug)? <i>Check the New Application and New Supplement Notification Checklists for a list of all classifications/properties at:</i> http://inside.fda.gov:9003/CDER/OfficeofBusinessProcessSupport/ucm163969.htm <i>If no, ask the document room staff to make the appropriate entries.</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Application Integrity Policy	YES	NO	NA	Comment
Is the application affected by the Application Integrity Policy (AIP)? <i>Check the AIP list at:</i> http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm	<input type="checkbox"/>	<input checked="" type="checkbox"/>		
<i>If yes, explain in comment column.</i>				
If affected by AIP, has OC/OMPQ been notified of the submission? If yes, date notified:	<input type="checkbox"/>	<input type="checkbox"/>	n/a	
User Fees	YES	NO	NA	Comment
Is Form 3397 (User Fee Cover Sheet)/Form 3792 (Biosimilar User Fee Cover Sheet) included with authorized signature?	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
<u>User Fee Status</u> <i>If a user fee is required and it has not been paid (and it is not exempted or waived), the application is unacceptable for filing following a 5-day grace period. Review stops. Send Unacceptable for Filing (UN) letter and contact user fee staff.</i>	Payment for this application (<i>check daily email from UserFeeAR@fda.hhs.gov</i>): <input checked="" type="checkbox"/> Paid <input type="checkbox"/> Exempt (orphan, government) <input type="checkbox"/> Waived (e.g., small business, public health) <input type="checkbox"/> Not required			
<i>If the firm is in arrears for other fees (regardless of whether a user fee has been paid for this application), the application is unacceptable for filing (5-day grace period does not apply). Review stops. Send UN letter and contact the user fee staff.</i>	Payment of other user fees: <input checked="" type="checkbox"/> Not in arrears <input type="checkbox"/> In arrears			
<u>User Fee Bundling Policy</u> <i>Refer to the guidance for industry, Submitting Separate Marketing Applications and Clinical Data for Purposes of Assessing User Fees at:</i> http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM079320.pdf	Has the user fee bundling policy been appropriately applied? <i>If no, or you are not sure, consult the User Fee Staff.</i> <input type="checkbox"/> Yes <input checked="" type="checkbox"/> No			
505(b)(2) (NDAs/NDA Efficacy Supplements only)	YES	NO	NA	Comment

Is the application a 505(b)(2) NDA? (Check the 356h form, cover letter, and annotated labeling). If yes , answer the bulleted questions below:	<input type="checkbox"/>	<input type="checkbox"/>	n/a	
• Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?	<input type="checkbox"/>	<input type="checkbox"/>	n/a	
• Is the application for a duplicate of a listed drug whose only difference is that the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action is less than that of the reference listed drug (RLD)? [see 21 CFR 314.54(b)(1)].	<input type="checkbox"/>	<input type="checkbox"/>	n/a	
• Is the application for a duplicate of a listed drug whose only difference is that the rate at which the proposed product's active ingredient(s) is absorbed or made available to the site of action is unintentionally less than that of the listed drug [see 21 CFR 314.54(b)(2)]? <i>If you answered yes to any of the above bulleted questions, the application may be refused for filing under 21 CFR 314.101(d)(9). Contact the 505(b)(2) review staff in the Immediate Office of New Drugs for advice.</i>	<input type="checkbox"/>	<input type="checkbox"/>	n/a	
• Is there unexpired exclusivity on another listed drug product containing the same active moiety (e.g., 5-year, 3-year, orphan, or pediatric exclusivity)? <i>Check the Electronic Orange Book at: http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm</i>	<input type="checkbox"/>	<input type="checkbox"/>	n/a	
If yes , please list below:				
Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration	
<i>If there is unexpired, 5-year exclusivity remaining on another listed drug product containing the same active moiety, a 505(b)(2) application cannot be submitted until the period of exclusivity expires (unless the applicant provides paragraph IV patent certification; then an application can be submitted four years after the date of approval.) Pediatric exclusivity will extend both of the timeframes in this provision by 6 months. 21 CFR 314.108(b)(2). Unexpired, 3-year exclusivity may block the approval but not the submission of a 505(b)(2) application.</i>				
Exclusivity	YES	NO	NA	Comment
Does another product (same active moiety) have orphan exclusivity for the same indication? <i>Check the Orphan Drug Designations and Approvals list at: http://www.accessdata.fda.gov/scripts/opdlisting/opd/index.cfm</i>	<input type="checkbox"/>	<input type="checkbox"/>		
If another product has orphan exclusivity , is the product considered to be the same product according to the orphan drug definition of sameness [see 21 CFR 316.3(b)(13)]? <i>If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
NDA/NDA efficacy supplements only: Has the applicant requested 5-year or 3-year Waxman-Hatch exclusivity? If yes , # years requested:	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	

<i>Note: An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.</i>				
NDAs only: Is the proposed product a single enantiomer of a racemic drug previously approved for a different therapeutic use?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
If yes, did the applicant: (a) elect to have the single enantiomer (contained as an active ingredient) not be considered the same active ingredient as that contained in an already approved racemic drug, and/or (b): request exclusivity pursuant to section 505(u) of the Act (per FDAAA Section 1113)? <i>If yes, contact the Orange Book Staff (CDER-Orange Book Staff).</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
BLAs only: Has the applicant requested 12-year exclusivity under section 351(k)(7) of the PHS Act? <i>If yes, notify Marlene Schultz-DePalo, OBP Biosimilars RPM</i> <i>Note: Exclusivity requests may be made for an original BLA submitted under Section 351(a) of the PHS Act (i.e., a biological reference product). A request may be located in Module 1.3.5.3 and/or other sections of the BLA and may be included in a supplement (or other correspondence) if exclusivity has not been previously requested in the original 351(a) BLA. An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	

Format and Content				
<i>Do not check mixed submission if the only electronic component is the content of labeling (COL).</i>	<input type="checkbox"/> All paper (except for COL) <input checked="" type="checkbox"/> All electronic <input type="checkbox"/> Mixed (paper/electronic)			
	<input checked="" type="checkbox"/> CTD <input type="checkbox"/> Non-CTD <input type="checkbox"/> Mixed (CTD/non-CTD)			
If mixed (paper/electronic) submission, which parts of the application are submitted in electronic format?				
Overall Format/Content	YES	NO	NA	Comment
If electronic submission, does it follow the eCTD guidance? ¹ If not, explain (e.g., waiver granted).	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Index: Does the submission contain an accurate comprehensive index?	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
Is the submission complete as required under 21 CFR 314.50 (NDAs/NDA efficacy supplements) or under 21 CFR 601.2 (BLAs/BLA efficacy supplements) including:	<input checked="" type="checkbox"/>	<input type="checkbox"/>		

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<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072349.pdf>

<input checked="" type="checkbox"/> legible <input checked="" type="checkbox"/> English (or translated into English) <input checked="" type="checkbox"/> pagination <input checked="" type="checkbox"/> navigable hyperlinks (electronic submissions only)				
If no, explain.				
BLAs only: Companion application received if a shared or divided manufacturing arrangement?	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	
If yes, BLA #				
Forms and Certifications				
<i>Electronic forms and certifications with electronic signatures (scanned, digital, or electronic – similar to DARRTS, e.g., /s/) are acceptable. Otherwise, paper forms and certifications with hand-written signatures must be included. Forms include: user fee cover sheet (3397/3792), application form (356h), patent information (3542a), financial disclosure (3454/3455), and clinical trials (3674); Certifications include: debarment certification, patent certification(s), field copy certification, and pediatric certification.</i>				
Application Form	YES	NO	NA	Comment
Is form FDA 356h included with authorized signature per 21 CFR 314.50(a)?	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
<i>If foreign applicant, a U.S. agent must sign the form [see 21 CFR 314.50(a)(5)].</i>				
Are all establishments and their registration numbers listed on the form/attached to the form?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Patent Information (NDAs/NDA efficacy supplements only)	YES	NO	NA	Comment
Is patent information submitted on form FDA 3542a per 21 CFR 314.53(c)?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Financial Disclosure	YES	NO	NA	Comment
Are financial disclosure forms FDA 3454 and/or 3455 included with authorized signature per 21 CFR 54.4(a)(1) and (3)?	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
<i>Forms must be signed by the APPLICANT, not an Agent [see 21 CFR 54.2(g)].</i>				
<i>Note: Financial disclosure is required for bioequivalence studies that are the basis for approval.</i>				
Clinical Trials Database	YES	NO	NA	Comment
Is form FDA 3674 included with authorized signature?	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
<i>If yes, ensure that the application is also coded with the supporting document category, "Form 3674."</i>				

<i>If no, ensure that language requesting submission of the form is included in the acknowledgement letter sent to the applicant</i>				
Debarment Certification	YES	NO	NA	Comment
Is a correctly worded Debarment Certification included with authorized signature? <i>Certification is not required for supplements if submitted in the original application; If foreign applicant, both the applicant and the U.S. Agent must sign the certification [per Guidance for Industry: Submitting Debarment Certifications].</i> <i>Note: Debarment Certification should use wording in FD&C Act Section 306(k)(1) i.e., “[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application.” Applicant may not use wording such as, “To the best of my knowledge...”</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Field Copy Certification (NDAs/NDA efficacy supplements only)	YES	NO	NA	Comment
For paper submissions only: Is a Field Copy Certification (that it is a true copy of the CMC technical section) included? <i>Field Copy Certification is not needed if there is no CMC technical section or if this is an electronic submission (the Field Office has access to the EDR)</i> <i>If maroon field copy jackets from foreign applicants are received, return them to CDR for delivery to the appropriate field office.</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Controlled Substance/Product with Abuse Potential	YES	NO	NA	Comment
<u>For NMEs:</u> Is an Abuse Liability Assessment, including a proposal for scheduling, submitted per 21 CFR 314.50(d)(5)(vii)? <i>If yes, date consult sent to the Controlled Substance Staff: 3/8/2015</i> <u>For non-NMEs:</u> <i>Date of consult sent to Controlled Substance Staff:</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Pediatrics	YES	NO	NA	Comment
<u>PREA</u> Does the application trigger PREA? <i>If yes, notify PeRC@fda.hhs.gov to schedule required PeRC meeting²</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>		

²

<http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/PediatricandMaternalHealthStaff/ucm027829.htm>

<i>Note: NDAs/BLAs/efficacy supplements for new active ingredients (including new fixed combinations), new indications, new dosage forms, new dosing regimens, or new routes of administration trigger PREA. All waiver & deferral requests, pediatric plans, and pediatric assessment studies must be reviewed by PeRC prior to approval of the application/supplement.</i>				
If the application triggers PREA, is there an agreed Initial Pediatric Study Plan (iPSP)?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<i>If no, may be an RTF issue - contact DPMH for advice.</i>				
If required by the agreed iPSP, are the pediatric studies outlined in the agreed iPSP completed and included in the application?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<i>If no, may be an RTF issue - contact DPMH for advice.</i>				
<u>BPCA:</u>				
Is this submission a complete response to a pediatric Written Request?	<input type="checkbox"/>	<input checked="" type="checkbox"/>		
<i>If yes, notify Pediatric Exclusivity Board RPM (pediatric exclusivity determination is required)³</i>				
Proprietary Name	YES	NO	NA	Comment
Is a proposed proprietary name submitted?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<i>If yes, ensure that the application is also coded with the supporting document category, "Proprietary Name/Request for Review."</i>				
REMS	YES	NO	NA	Comment
Is a REMS submitted?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<i>If yes, send consult to OSE/DRISK and notify OC/OSI/DSC/PMSB via the CDER OSI RMP mailbox</i>				
Prescription Labeling	<input type="checkbox"/> Not applicable			
Check all types of labeling submitted.	<input checked="" type="checkbox"/> Package Insert (PI) <input checked="" type="checkbox"/> Patient Package Insert (PPI) <input checked="" type="checkbox"/> Instructions for Use (IFU) <input checked="" type="checkbox"/> Medication Guide (MedGuide) <input checked="" type="checkbox"/> Carton labels <input checked="" type="checkbox"/> Immediate container labels <input type="checkbox"/> Diluent <input type="checkbox"/> Other (specify)			
	YES	NO	NA	Comment
Is Electronic Content of Labeling (COL) submitted in SPL format?	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
<i>If no, request applicant to submit SPL before the filing date.</i>				

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<http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/PediatricandMaternalHealthStaff/ucm027837.htm>

Version: 3/20/2014

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Is the PI submitted in PLR format? ⁴	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
If PI not submitted in PLR format , was a waiver or deferral requested before the application was received or in the submission? If requested before application was submitted , what is the status of the request? <i>If no waiver or deferral, request applicant to submit labeling in PLR format before the filing date.</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
For applications submitted on or after June 30, 2015: Is the PI submitted in PLLR format? ⁵	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
If PI not submitted in PLLR format , was a waiver or deferral requested before the application was received or in the submission? If requested before application was submitted , what is the status of the request? <i>If no waiver or deferral, request applicant to submit labeling in PLR/PLLR format before the filing date.</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
All labeling (PI, PPI, MedGuide, IFU, carton and immediate container labels) consulted to OPDP?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
MedGuide, PPI, IFU (plus PI) consulted to OSE/DRISK? (send WORD version if available)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Carton and immediate container labels, PI, PPI sent to OSE/DMEPA and appropriate CMC review office (OBP or ONDQA)?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
OTC Labeling	<input checked="" type="checkbox"/> Not Applicable			
Check all types of labeling submitted.	<input type="checkbox"/> Outer carton label <input type="checkbox"/> Immediate container label <input type="checkbox"/> Blister card <input type="checkbox"/> Blister backing label <input type="checkbox"/> Consumer Information Leaflet (CIL) <input type="checkbox"/> Physician sample <input type="checkbox"/> Consumer sample <input type="checkbox"/> Other training kit cartoon and training kit label			
	YES	NO	NA	Comment
Is electronic content of labeling (COL) submitted? <i>If no, request in 74-day letter.</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
Are annotated specifications submitted for all stock keeping units (SKUs)?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	

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<http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/StudyEndpointsandLabelingDevelopmentTeam/ucm025576.htm>

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<http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/StudyEndpointsandLabelingDevelopmentTeam/ucm025576.htm>

<i>If no, request in 74-day letter.</i>				
If representative labeling is submitted, are all represented SKUs defined?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<i>If no, request in 74-day letter.</i>				
All labeling/packaging sent to OSE/DMEPA?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Other Consults	YES	NO	NA	Comment
Are additional consults needed? (e.g., IFU to CDRH; QT study report to QT Interdisciplinary Review Team)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	CDRH 3/8/2015 CDRH compliance 3/8/2015
<i>If yes, specify consult(s) and date(s) sent:</i>				
Meeting Minutes/SPAs	YES	NO	NA	Comment
End-of Phase 2 meeting(s)? Date(s): July 24, 2008	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
<i>If yes, distribute minutes before filing meeting</i>				
Pre-NDA/Pre-BLA/Pre-Supplement meeting(s)? Date(s): 10/8/2014	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
<i>If yes, distribute minutes before filing meeting</i>				
Any Special Protocol Assessments (SPAs)? Date(s): SPA agreement letter 06/07/2010, SPA agreement letter 10/30/2011; SPA agreement letter 07/12/2012; SPA modification no agreement letter 04/29/2014	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
<i>If yes, distribute letter and/or relevant minutes before filing meeting</i>				

ATTACHMENT

MEMO OF FILING MEETING

DATE: 4/6/2015

BACKGROUND: ZINBRYTA™ (daclizumab High Yield Process) 150 mg/mL Injection
Sponsor: AbbVie Inc. NME BLA "The Program" submitted on 2/27/2015

REVIEW TEAM:

Discipline/Organization	Names		Present at filing meeting? (Y or N)
Regulatory Project Management	RPM:	Su-Lin Sun	Y
	CPMS/TL:	Jackie Ware	N
Cross-Discipline Team Leader (CDTL)	John Marler		Y
Division Director/Deputy	Billy Dunn		Y
Office Director/Deputy	Ellis Unger		Y
Clinical	Reviewer:	Lawrence Rodichok	Y
	TL:	John Marler	Y
Social Scientist Review (<i>for OTC products</i>)	Reviewer:	N/A	
	TL:		
OTC Labeling Review (<i>for OTC products</i>)	Reviewer:	NA	
	TL:		
Clinical Microbiology (<i>for antimicrobial products</i>)	Reviewer:	NA	
	TL:		
Clinical Pharmacology	Reviewer:	Ta-Chen Wu	Y
	TL:	Angela Men	Y
Biostatistics	Reviewer:	Xiang Ling	Y
	TL:	Kun Jin	Y

Nonclinical (Pharmacology/Toxicology)	Reviewer:	Davis Carbone	Y
	TL:	Lois Freed (covered by Barbara Wilcox)	Y
Statistics (carcinogenicity)	Reviewer:	N/A	
	TL:		
Immunogenicity (assay/assay validation) <i>(for protein/peptide products only)</i>	Reviewer:	N/A	
	TL:		
Product Quality (CMC)	Reviewer:	Chen Sun	Y
	TL:	Joel Welch	Y
Biopharmaceutics	Reviewer	N/A	
	TL:		
Quality Microbiology	Reviewer:	Colleen Thomas	Y
	TL:	Patricia Hughes	N
CMC Labeling Review	Reviewer:	Jibril Abdus-Samad	N
	TL:		
Facility Review/Inspection	Reviewer:	Wayne Seifert	Y
	TL:	Zhihao Peter Qiu	N
OSE/DMEPA (proprietary name, carton/container labels))	Reviewer:	Justine Harris	Y
	TL:	Danielle Harris	N
OSE/DRISK (REMS)	Reviewer:	Robert Pratt	Y
	TL:	Jamie Wilkins-Parker	Y
OC/OSI/DSC/PMSB (REMS)	Reviewer:	Kendra Biddick	N
	TL:		

Bioresearch Monitoring (OSI)	Reviewer:	Anthony El Hage	Y
	TL:	Susan Thompson	N
Controlled Substance Staff (CSS)	Reviewer:	Joshua Hunt	Y
	TL:	Michael Klein	N
DMPH (Peds)	Reviewer:	Donna Snyder Denise Pica-Branco (PM)	Y
	TL:	Hari Sachs	N
CDRH	Reviewer:	Lana Shiu	Y
	TL:	Ryan McGowan	N
OCP	TL	Patricia Love	Y
DEPI	Reviewer:	Lockwood Taylor	Y
	TL:		
DPV	Reviewer:	Monica Munoz	N
	TL:	Corrinne Kulick	Y
DMPP	Reviewer:	Sharon Williams	Y
	TL:	Melissa Hulett	N
OPDP	Reviewer:	Aline Moukhtara	Y
	TL:		
ALD (Associated Labeling Director)	Nicole Bradley		Y

FILING MEETING DISCUSSION:

<p>GENERAL</p> <ul style="list-style-type: none"> • 505(b)(2) filing issues: <ul style="list-style-type: none"> ○ Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA? ○ Did the applicant provide a scientific “bridge” demonstrating the relationship between the proposed product and the 	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO <input type="checkbox"/> YES <input type="checkbox"/> NO
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<p>referenced product(s)/published literature?</p> <p>Describe the scientific bridge (e.g., BA/BE studies):</p>	
<ul style="list-style-type: none"> Per reviewers, are all parts in English or English translation? <p>If no, explain:</p>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> Electronic Submission comments <p>List comments: CDISC issue (per safety team); missing PK data files, missing patient profiles from original submission dated 2/27/15, sponsor submitted partial data on 4/2/15.</p>	<input type="checkbox"/> Not Applicable <input type="checkbox"/> No comments
<p>CLINICAL</p> <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> Clinical study site(s) inspections(s) needed? <p>If no, explain:</p>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> Advisory Committee Meeting needed? <p>Comments:</p> <p><i>If no, for an NME NDA or original BLA, include the reason. For example:</i></p> <ul style="list-style-type: none"> <i>this drug/biologic is not the first in its class</i> <i>the clinical study design was acceptable</i> <i>the application did not raise significant safety or efficacy issues</i> <i>the application did not raise significant public health questions on the role of the drug/biologic in the diagnosis, cure, mitigation, treatment or prevention of a disease</i> 	<input type="checkbox"/> YES Date if known: <input checked="" type="checkbox"/> NO <input type="checkbox"/> To be determined Reason: TBD
<ul style="list-style-type: none"> If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance? 	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO

Comments:	
CONTROLLED SUBSTANCE STAFF <ul style="list-style-type: none"> Abuse Liability/Potential Comments:	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
CLINICAL MICROBIOLOGY Comments:	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
CLINICAL PHARMACOLOGY Comments:	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> Clinical pharmacology study site(s) inspections(s) needed? 	<input type="checkbox"/> YES <input checked="" type="checkbox"/> NO
BIOSTATISTICS Comments:	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
NONCLINICAL (PHARMACOLOGY/TOXICOLOGY) Comments:	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
IMMUNOGENICITY (protein/peptide products only) Comments:	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
PRODUCT QUALITY (CMC) Comments:	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
New Molecular Entity (NDAs only)	

<ul style="list-style-type: none"> Is the product an NME? 	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<p><u>Environmental Assessment</u></p> <ul style="list-style-type: none"> Categorical exclusion for environmental assessment (EA) requested? <p>If no, was a complete EA submitted?</p> <p>If EA submitted, consulted to EA officer (OPS)?</p> <p>Comments:</p>	<input type="checkbox"/> YES <input checked="" type="checkbox"/> NO <input type="checkbox"/> YES <input type="checkbox"/> NO <input type="checkbox"/> YES <input type="checkbox"/> NO
<p><u>Quality Microbiology</u></p> <ul style="list-style-type: none"> Was the Microbiology Team consulted for validation of sterilization? <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<p><u>Facility Inspection</u></p> <ul style="list-style-type: none"> Establishment(s) ready for inspection? Establishment Evaluation Request (EER/TBP-EER) submitted to OMPQ? <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO <input type="checkbox"/> YES <input type="checkbox"/> NO
<p><u>Facility/Microbiology Review (BLAs only)</u></p> <p>Comments: will have IR comments to be sent to sponsor</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p><u>CMC Labeling Review</u></p> <p>Comments:</p>	<input checked="" type="checkbox"/> FILE <input type="checkbox"/> Review issues for 74-day letter

<p>APPLICATIONS IN THE PROGRAM (PDUFA V) (NME NDAs/Original BLAs)</p> <ul style="list-style-type: none"> • Were there agreements made at the application's pre-submission meeting (and documented in the minutes) regarding certain late submission components that could be submitted within 30 days after receipt of the original application? • If so, were the late submission components all submitted within 30 days? 	<input type="checkbox"/> N/A <input type="checkbox"/> YES <input checked="" type="checkbox"/> NO <input type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> • What late submission components, if any, arrived after 30 days? 	<p>Patient profile submitted on 4/2/15 based on FDA's IR request</p>
<ul style="list-style-type: none"> • Was the application otherwise complete upon submission, including those applications where there were no agreements regarding late submission components? 	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> • Is a comprehensive and readily located list of all clinical sites included or referenced in the application? 	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> • Is a comprehensive and readily located list of all manufacturing facilities included or referenced in the application? 	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
REGULATORY PROJECT MANAGEMENT	
<p>Signatory Authority: Dr. Robert Temple</p> <p>Date of Mid-Cycle Meeting (for NME NDAs/BLAs in "the Program" PDUFA V): July 27, 2015</p> <p>21st Century Review Milestones (see attached) (listing review milestones in this document is optional): TBD</p> <p>Comments:</p>	
REGULATORY CONCLUSIONS/DEFICIENCIES	
<input type="checkbox"/>	<p>The application is unsuitable for filing. Explain why:</p>
<input checked="" type="checkbox"/>	<p>The application, on its face, appears to be suitable for filing.</p>

	<p><u>Review Issues:</u></p> <p><input checked="" type="checkbox"/> No review issues have been identified for the 74-day letter.</p> <p><input type="checkbox"/> Review issues have been identified for the 74-day letter.</p> <p><u>Review Classification:</u></p> <p><input checked="" type="checkbox"/> Standard Review</p> <p><input type="checkbox"/> Priority Review</p>
ACTIONS ITEMS	
<input type="checkbox"/>	Ensure that any updates to the review priority (S or P) and classifications/properties are entered into tracking system (e.g., chemical classification, combination product classification, orphan drug).
<input type="checkbox"/>	If RTF, notify everyone who already received a consult request, OSE PM, and Product Quality PM (to cancel EER/TBP-EER).
<input type="checkbox"/>	If filed, and the application is under AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.
<input type="checkbox"/>	351(k) BLA/supplement: If filed, send filing notification letter on day 60
<input type="checkbox"/>	If priority review: <ul style="list-style-type: none"> • notify sponsor in writing by day 60 (see CST for choices) • notify OMPQ (so facility inspections can be scheduled earlier)
<input type="checkbox"/>	Send review issues/no review issues by day 74
<input type="checkbox"/>	Conduct a PLR format labeling review and include labeling issues in the 74-day letter
<input type="checkbox"/>	Update the PDUFA V DARRTS page (for applications in the Program)
<input type="checkbox"/>	Other

Annual review of template by OND ADRAAs completed: September 2014

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

/s/

LAURIE A KELLEY
05/06/2015