

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**761067Orig1s000**

**OTHER REVIEW(S)**

**PMR/PMC DEVELOPMENT TEMPLATE**  
For 506B Reportable<sup>1</sup> PMRs and PMCs only


This form describes and provides the rationale for postmarketing requirements/commitments (PMRs/PMCs) subject to reporting requirements under section 506B of the FDCA.

Complete this form using the [instructions](#) (see Appendix A) and by referring to [MAPP 6010.9](#), “Procedures and Responsibilities for Developing Postmarketing Commitments and Requirements.”

**Note:** Do *not* use this template for CMC PMCs. Instead, use the CMC PMC Development Template.<sup>1</sup>

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**SECTION A: Administrative Information**

NDA/BLA/Supplement # 761067  
PMR/PMC Set (####-#)   
Product Name: Ilumya™ (tildrakizumab) injection, for subcutaneous use  
Applicant Name: Merck Sharp & Dohme Corporation  
ODE/Division: ODE 3/DDDP

**SECTION B: PMR/PMC Information**

**1. PMR/PMC Description**

Conduct a retrospective cohort study using claims or electronic medical record data or a case control study to assess major congenital malformations, spontaneous abortions, stillbirths, small for gestational age, neonatal deaths, and infant infections in women exposed to tildrakizumab during pregnancy compared to an unexposed control population.

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**2. PMR/PMC Schedule Milestones<sup>2, 3</sup>**

Draft Protocol Submission: 02/2019  
Final Protocol Submission: 08/2019  
Study/Trial Completion: 01/2026  
Interim /Other:  
Final Report Submission: 01/2027

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<sup>1</sup> 506B “reportable” includes all studies/trials an applicant has agreed upon or is required to conduct related to clinical safety, clinical efficacy, clinical pharmacology, or nonclinical toxicology (21 CFR 314.81(b)(2)(vii) and 21 CFR 601.70(a)). All PMRs are considered 506 “reportable.” A separate development template is used for 506 B non-reportable (e.g., chemistry, manufacturing, and controls (CMC)) PMCs, which is located in the CST.

<sup>2</sup> Final protocol, study/trial completion, and final report submissions are required milestones. Draft protocol submissions and interim milestones are optional. EXCEPTION: PMRs/PMCs for medical countermeasures may have only draft/final protocol submission dates and no other milestones, since the study/trial will only be initiated in the event of an emergency. Interim milestones may include interim report milestones for studies/trials that may be of long duration. May include interim subject accrual milestone (e.g., for accelerated approval PMRs). Other milestones should be justified in Section D, question 3.

<sup>3</sup> Dates should be numerical (e.g., 05/2016). PREA PMR date format may be MM/DD/YYYY if a day is specified.

## **SECTION C: PMR/PMC Rationale**

### **1. Describe the particular review issue and the goal of the study<sup>4</sup> or clinical trial<sup>5</sup> in the text box below.**

Trials in adults with moderate-to-severe plaque psoriasis who are candidates for systemic therapy or phototherapy are completed and the product is ready for approval. Pregnant women were excluded from the development program and data is needed in this population.

### **2. Explain why this issue can be evaluated post-approval and does not need to be addressed prior to approval. (Select one explanation below.)**

- ☐ Subpart I or H (animal efficacy rule) PMR: Approved under Subpart I or H (animal efficacy rule) authorities; postmarketing study/trial required to verify and describe clinical benefit [\[Skip to Q.5\]](#)
- ☐ Subpart H or E (accelerated approval) PMR: Approved under Subpart H or E (accelerated approval) authorities; postmarketing study/trial required to verify and describe clinical benefit [\[Skip to Q.5\]](#)
- ☐ PREA PMR: Meets PREA postmarketing pediatric study requirements [\[Skip to Q.5\]](#)
- ☒ FDAAA PMR (safety): Benefit/risk profile of the drug appears favorable; however, there are uncertainties about aspects of the drug's safety profile. Because the investigation will evaluate a serious risk, it meets FDAAA requirements for a postmarketing safety study or trial [\[Go to Q.3\]](#)
- ☐ PMC (506B reportable): Benefit/risk profile of the drug appears favorable; however, there are uncertainties about aspects of the drug's efficacy profile or other issues. The purpose of the investigation does not meet requirements under Subpart I/H, H/E, PREA, or FDAAA to be a PMR, and therefore the investigation is a PMC. [\[Go to Q.3\]](#)

### **3. For FDAAA PMRs and 506B PMCs only**

**The study or trial can be conducted post-approval because:** [\[Select all that apply\]](#)

- ☐ Longer-term data needed to further characterize the safety/efficacy of the drug
- ☐ Based on the purpose and/or design, it is only feasible to conduct the study/trial post-approval
- ☒ Prior clinical experience (e.g., with other drugs in the class) indicates adequate safety or efficacy data to support approval, but some uncertainties about safety or efficacy remain and should be further characterized
- ☒ Only a small subpopulation is affected (e.g., patients with severe renal impairment) and effects of the drug in the subpopulation can be further evaluated after approval
- ☐ Study/trial is to further explore a theoretical concern that does not impact the approval determination
- ☐ Other reason (describe in text box below)

[\[If you selected "other reason," expand on the reason\(s\) why it is appropriate to conduct the study/trial\]](#)

<sup>4</sup> A "study" is an investigation that is not a clinical trial, such as an observational (epidemiologic) study, animal study, or laboratory experiment.

<sup>5</sup> A "clinical trial" is any prospective investigation in which the applicant or investigator determines the method of assigning the drug product(s) or other interventions to one or more human subjects. Note that under PREA, clinical trials involving pediatric patients are specifically referred to as "studies."

postapproval and why the issue does not need to be addressed *prior to* approval.]

4. **For FDAAA PMRs only** *[for PMCs skip to Q.5]. Complete this entire section*

a. **The purpose of the study/clinical trial is to:** *[Select one, then go to Q.4.b]*

- ☐ Assess a known serious risk related to the use of the drug
- ☐ Assess a signal 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

**Complete Q4.b if the necessary data can only be obtained through a particular type of nonclinical study or clinical pharmacology trial. Otherwise complete Q4.c and Q4.d.**

b. **FAERS<sup>6</sup> and Sentinel's postmarket ARIA<sup>7</sup> system are not sufficient for the purposes described in Q1. and Q4.a because the safety issue involves:**

*[Select all that apply then to skip to Q.5. If none apply, answer both Q4.c and Q4.d]*

- ☐ A serious risk of genotoxicity, carcinogenicity, or reproductive toxicity, and these signals are initially best assessed through in vitro or animal studies.
- ☐ A potential drug interaction resulting in lower/higher drug exposure and resultant serious drug risks, and accurate assessment of an interaction is feasible only through in vitro mechanistic studies or clinical pharmacokinetic and pharmacodynamics trials.
- ☐ The potential for lower/higher drug exposure and resultant serious drug risks in patients with hepatic or renal impairment, or other metabolic abnormalities, and accurate assessment is feasible only through in vitro mechanistic studies or clinical pharmacokinetic and pharmacodynamics trials.
- ☐ An immunologic concern for which accurate assessment requires in vitro development or validation of specific assays.

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<sup>6</sup> FDA Adverse Event Reporting System (FAERS)

<sup>7</sup> Active Risk Identification and Analysis (ARIA)

*Complete Q4.c when FAERS cannot provide the necessary data and Q4.b does not apply*

**c. FAERS data cannot be used to fully characterize the serious risk of interest because:**

*[Select all that apply then go to Q.4.d ]*

- ☒ Assessment of the serious risk necessitates calculation of the rate of occurrence (e.g., incidence or odds ratio) of the adverse event(s), and FAERS data cannot be used for such a calculation.
- ☐ The serious risk of concern has a delayed time to onset, or delayed time to detection after exposure (e.g., cancer), and FAERS data are more useful for detecting events that are closely linked in time to initiation of drug therapy.
- ☐ The serious risk of concern occurs commonly in the population (e.g., myocardial infarction) and FAERS data are more useful in detecting rare serious adverse events for which the background rates are low.
- ☐ Other

[If you selected "other," expand on the reason(s) why FAERS is not sufficient.]

*Complete Q4.d when the ARIA system cannot provide the necessary data and Q4.b does not apply.*

**d. The currently available data within the ARIA system cannot be used to fully characterize the serious risk of interest because:** *[Select all that apply then go to Q.4.e ]*

- ☐ Cannot identify exposure to the drug(s) of interest in the database.
- ☐ Serious risk (adverse event) of concern cannot be identified in the database.
- ☒ The population(s) of interest cannot be identified in the database.
- ☐ Long-term follow-up information required to assess the serious risk are not available in the database.
- ☒ Important confounders or covariates are not available or well represented in the database.
- ☐ The database does not contain an adequate number of exposed patients to provide sufficient statistical power to analyze the association between the drug and the serious risk of concern.
- ☐ The purpose of the evaluation is to rule out a modest relative risk, and observational studies, such as an ARIA analysis, are not well suited for such use.
- ☐ Other

[If you selected "other," expand on the reason(s) why ARIA is not sufficient.]

- e. If FAERS and the ARIA system are not sufficient for the purpose in Q1. and Q4.a, is a study sufficient?  
[Select either “Yes” or “No” and provide the appropriate responses.]

☒ Yes, a study is sufficient [Explain your answer in the textbox and then go to Q.5]

A study such as a retrospective cohort study that uses claims or electronic medical record data or a case control study could be used to achieve this purpose if the study is designed to include an unexposed control population.

☐ No, a study is not sufficient [Select all explanations that apply then go to Q.4.f]

- ☐ Need to minimize bias and/or confounding via randomization
- ☐ Need for placebo control
- ☐ Need to capture detailed information about covariates or confounders that are either not routinely collected during the usual course of medical practice, or are not collected at the frequency needed for assessment of the safety issue (e.g. hourly blood glucose measures, etc.).
- ☐ Need pre-specified and prospective active data collection of the outcome/endpoint of interest
- ☐ Other

- f. ☐ Because a study is not sufficient, a clinical trial is required. [Go to Q.5]

5. **For all PMRs and PMCs:** What type of study or clinical trial is needed to achieve the goal described in Q1 or Q4.a above?

[Select ONE OPTION only under either “Type of Study” or “Type of clinical Trial”]

**TYPE OF STUDY**

- ☐ Drug interaction or bioavailability studies (nonclinical only)
- ☒ Epidemiologic (observational) study related to safe drug use
- ☐ Epidemiologic (observational) study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
- ☐ Immunogenicity study (nonclinical)
- ☐ Meta-analysis or pooled analysis of previous observational studies
- ☐ Nonclinical (animal) study (e.g., genotoxicity, carcinogenicity, reproductive toxicology)
- ☐ Nonclinical (in vitro) study (laboratory/microbiology resistance, receptor affinity)
- ☐ Pharmacogenetic or pharmacogenomic study
- ☐ Pharmacokinetic (PK) and/or pharmacodynamics (PD) study (nonclinical only)
- ☐ Quality CMC study (e.g., manufacturing, studies on impurities)
- ☐ Quality stability study

#### TYPE OF STUDY

- ☐ Registry-based observational study  
☐ Other (describe) \_\_\_\_\_

#### TYPE OF CLINICAL TRIAL

- ☐ Combined PK/PD, safety and/or efficacy trial (*PREA\* PMRs only*)  
☐ Dose-response clinical trial  
☐ Dosing trial (e.g., alternative dosing schedule)  
☐ Drug interaction or bioavailability clinical trial (clinical only)  
☐ Immunogenicity trial (clinical)  
☐ Meta-analysis or pooled analysis of previous clinical trials  
☐ Pharmacogenetic or pharmacogenomic clinical trial  
☐ Pharmacokinetic (PK) and/or pharmacodynamic (PD) clinical trial  
☐ Primary efficacy clinical trial (i.e., with a primary efficacy endpoint; to further define efficacy; may include secondary safety endpoints)  
☐ Primary safety clinical trial (e.g., to evaluate the long-term safety of a drug; to evaluate drug toxicity in a subpopulation; may include secondary efficacy endpoints) – *excludes SOT*  
☐ Safety outcomes trial (SOT)\*\*  
☐ Thorough Q-T clinical trial  
☐ Other (describe) \_\_\_\_\_

\* Note that under PREA, clinical trials involving pediatric patients are specifically referred to as “studies.” However, for the purposes of this template, PREA investigations are categorized according to the established definitions of “studies” and “trials” (see Footnotes 3 and 4).

\*\* A safety outcomes trial (SOT) is defined as a large, prospective, randomized, controlled trial that is specifically designed and adequately powered to test a safety hypothesis using a clinical outcome, generally irreversible morbidity or mortality, as the primary trial endpoint. A cardiovascular outcomes trial (CVOT) is an example of an SOT.

#### SECTION D: PMR/PMC Additional Information

**1. This PMR/PMC applies to other drugs or applications (e.g. drugs in a therapeutic class; different formulations of the same drug).**

- ☐ Yes  
☒ No

**2. This study or clinical trial focuses on the following special population(s) or circumstance(s):**

*[Select all that apply]*

- ☐ For *non-PREA* pediatric studies/trials only: Pediatric population
- ☐ Geriatric population
- ☐ Lactating/nursing mothers
- ☐ Medical Countermeasures (e.g. anthrax exposure, bioterrorism)
- ☐ Orphan or rare disease population
- ☒ Pregnant women
- ☐ Racial/ethnic population
- ☐ Not applicable

**3. (Complete if applicable) Additional comments about the PMR/PMC** (e.g., points or concerns not previously described; explanation for inclusion of milestones other than the 3 “core” milestones or draft protocol submission)

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**SECTION E: PMR/PMC Development Coordinator Statements<sup>8</sup>Error! Reference source not found.**

**1. The PMR/PMC is clear, feasible, and appropriate<sup>9</sup> because:** *[Select all that apply]*

- ☒ The study/clinical trial meets criteria for a PMR or a PMC.
- ☒ The objectives of the study/clinical trial are clear from the description of the PMR/PMC.
- ☐ The applicant has adequately justified the choice of milestone dates.
- ☐ The applicant has had sufficient time to review the PMR/PMC, ask questions, determine feasibility, and contribute to the development process.

**2. ☐ (If the PMR/PMC is a randomized controlled clinical trial) The following ethical considerations were made with regard to:**

- There is a significant question about the public health risks of the drug.
- There is not enough existing information to assess the public health risks of the drug.
- Information about the public health risks cannot be gained through a different kind of investigation.
- The trial will be appropriately designed to answer question about a drug’s efficacy or safety.

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<sup>8</sup> This section is completed by the PMR/PMC Development Coordinator, who is usually the OND division’s Deputy Director for Safety (DDS). See DEFINITIONS section of CDER MAPP 6010.9, *Procedures and Responsibilities for Developing Postmarketing Requirements and Commitments*.

<sup>9</sup> See POLICY section of CDER MAPP 6010.9.



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

3. ☒ **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.**

Insert electronic signature (usually the Deputy Director for Safety)

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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.**  
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/s/  
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DAWN WILLIAMS  
03/20/2018

TATIANA OUSSOVA  
03/21/2018

**PMR/PMC DEVELOPMENT TEMPLATE**  
For 506B Reportable<sup>1</sup> PMRs and PMCs only


This form describes and provides the rationale for postmarketing requirements/commitments (PMRs/PMCs) subject to reporting requirements under section 506B of the FDCA.

**Complete this form using the [instructions](#) (see Appendix A) and by referring to [MAPP 6010.9](#), “Procedures and Responsibilities for Developing Postmarketing Commitments and Requirements.”**

**Note: Do *not* use this template for CMC PMCs. Instead, use the CMC PMC Development Template.<sup>1</sup>**

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**SECTION A: Administrative Information**

**NDA/BLA/Supplement #**            **761067**  
**PMR/PMC Set (####-#)**              
**Product Name:**                    **Ilumya™ (tildrakizumab) injection, for subcutaneous use**  
**Applicant Name:**                **Merck Sharp & Dohme Corporation**  
**ODE/Division:**                  **ODE 3/DDDP**

**SECTION B: PMR/PMC Information**

**1. PMR/PMC Description**

Conduct an observational study to assess the long-term safety of tildrakizumab compared to other therapies used in the treatment of adults with moderate-to-severe plaque psoriasis who are candidates for systemic therapy or phototherapy in the course of actual clinical care. The study’s primary outcome is long-term malignancy. Secondary outcomes include, but are not limited to, serious infections, tuberculosis, opportunistic infections, hypersensitivity reactions, autoimmune disease, neurologic or demyelinating disease, cardiovascular, gastrointestinal and hematologic adverse events.

Describe and justify the choice of appropriate comparator population(s) and estimated background rate(s) relative to tildrakizumab-exposed patients; clearly define the primary comparator population for the primary objective. Design the study around a testable hypothesis to assess, with sufficient sample size and power, a clinically meaningful increase in malignancy risk above the comparator background rate(s), with a pre-specified statistical analysis method. Specify concise case definitions and validation algorithms for both primary and secondary outcomes. For the tildrakizumab-exposed and comparator(s) cohorts, clearly define the study drug initiation period and any exclusion and inclusion criteria. Enroll patients over an initial 4 year period and follow for a minimum of 8 years from the time of enrollment.

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**2. PMR/PMC Schedule Milestones<sup>2, 3</sup>**

<sup>1</sup> 506B “reportable” includes all studies/trials an applicant has agreed upon or is required to conduct related to clinical safety, clinical efficacy, clinical pharmacology, or nonclinical toxicology (21 CFR 314.81(b)(2)(vii) and 21 CFR 601.70(a)). All PMRs are considered 506 “reportable.” A separate development template is used for 506 B non-reportable (e.g., chemistry, manufacturing, and controls (CMC)) PMCs, which is located in the CST.

<sup>2</sup> *Final protocol, study/trial completion, and final report* submissions are required milestones. *Draft protocol submissions* and *interim* milestones are optional. EXCEPTION: PMRs/PMCs for medical countermeasures may have only draft/final protocol submission dates and no other milestones,

Draft Protocol Submission:	02/2019
Final Protocol Submission:	02/2020
Study/Trial Completion:	02/2033
Interim /Other:	
Final Report Submission:	02/2034

### **SECTION C: PMR/PMC Rationale**

#### **1. Describe the particular review issue and the goal of the study<sup>4</sup> or clinical trial<sup>5</sup> in the text box below.**

There is a concern that this new biologic product may increase the risk of malignancies and serious infections due to its immunosuppressive effect.

#### **2. Explain why this issue can be evaluated post-approval and does not need to be addressed prior to approval. (Select one explanation below.)**

- ☐ **Subpart I or H (animal efficacy rule) PMR:** Approved under Subpart I or H (animal efficacy rule) authorities; postmarketing study/trial required to verify and describe clinical benefit [\[Skip to Q.5\]](#)
- ☐ **Subpart H or E (accelerated approval) PMR:** Approved under Subpart H or E (accelerated approval) authorities; postmarketing study/trial required to verify and describe clinical benefit [\[Skip to Q.5\]](#)
- ☐ **PREA PMR:** Meets PREA postmarketing pediatric study requirements [\[Skip to Q.5\]](#)
- ☒ **FDAAA PMR (safety):** Benefit/risk profile of the drug appears favorable; however, there are uncertainties about aspects of the drug's safety profile. Because the investigation will evaluate a serious risk, it meets FDAAA requirements for a postmarketing safety study or trial [\[Go to Q.3\]](#)
- ☐ **PMC (506B reportable):** Benefit/risk profile of the drug appears favorable; however, there are uncertainties about aspects of the drug's efficacy profile or other issues. The purpose of the investigation does not meet requirements under Subpart I/H , H/E, PREA, or FDAAA to be a PMR, and therefore the investigation is a PMC. [\[Go to Q.3\]](#)

#### **3. For FDAAA PMRs and 506B PMCs only**

**The study or trial can be conducted post-approval because:** [\[Select all that apply\]](#)

- ☒ Longer-term data needed to further characterize the safety/efficacy of the drug
- ☐ Based on the purpose and/or design, it is only feasible to conduct the study/trial post-approval
- ☒ Prior clinical experience (e.g., with other drugs in the class) indicates adequate safety or efficacy data to support approval, but some uncertainties about safety or efficacy remain and should be further characterized

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since the study/trial will only be initiated in the event of an emergency. Interim milestones may include interim report milestones for studies/trials that may be of long duration. May include interim subject accrual milestone (e.g., for accelerated approval PMRs). Other milestones should be justified in Section D, question 3.

<sup>3</sup> Dates should be numerical (e.g., 05/2016). PREA PMR date format may be MM/DD/YYYY if a day is specified.

<sup>4</sup> A "study" is an investigation that is not a clinical trial, such as an observational (epidemiologic) study, animal study, or laboratory experiment.

<sup>5</sup> A "clinical trial" is any prospective investigation in which the applicant or investigator determines the method of assigning the drug product(s) or other interventions to one or more human subjects. Note that under PREA, clinical trials involving pediatric patients are specifically referred to as "studies."

- ☐ Only a small subpopulation is affected (e.g., patients with severe renal impairment) and effects of the drug in the subpopulation can be further evaluated after approval
- ☐ Study/trial is to further explore a theoretical concern that does not impact the approval determination
- ☐ Other reason (describe in text box below)

[If you selected “other reason,” expand on the reason(s) why it is appropriate to conduct the study/trial postapproval and why the issue does not need to be addressed *prior to* approval.]

4. **For FDAAA PMRs only** *[for PMCs skip to Q.5]. Complete this entire section*

a. **The purpose of the study/clinical trial is to:** *[Select one, then go to Q.4.b]*

- ☐ Assess a known serious risk related to the use of the drug
- ☐ Assess a signal 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

*Complete Q4.b if the necessary data can only be obtained through a particular type of nonclinical study or clinical pharmacology trial. Otherwise complete Q4.c and Q4.d.*

b. **FAERS<sup>6</sup> and Sentinel’s postmarket ARIA<sup>7</sup> system are not sufficient for the purposes described in Q1. and Q4.a because the safety issue involves:**

*[Select all that apply then to skip to Q.5. If none apply, answer both Q4.c and Q4.d]*

- ☐ A serious risk of genotoxicity, carcinogenicity, or reproductive toxicity, and these signals are initially best assessed through in vitro or animal studies.
- ☐ A potential drug interaction resulting in lower/higher drug exposure and resultant serious drug risks, and accurate assessment of an interaction is feasible only through in vitro mechanistic studies or clinical pharmacokinetic and pharmacodynamics trials.
- ☐ The potential for lower/higher drug exposure and resultant serious drug risks in patients with hepatic or renal impairment, or other metabolic abnormalities, and accurate assessment is feasible only through in vitro mechanistic studies or clinical pharmacokinetic and pharmacodynamics trials.
- ☐ An immunologic concern for which accurate assessment requires in vitro development or validation of specific assays.

<sup>6</sup> FDA Adverse Event Reporting System (FAERS)

<sup>7</sup> Active Risk Identification and Analysis (ARIA)

*Complete Q4.c when FAERS cannot provide the necessary data and Q4.b does not apply*

**c. FAERS data cannot be used to fully characterize the serious risk of interest because:**

*[Select all that apply then go to Q.4.d ]*

- ☐ Assessment of the serious risk necessitates calculation of the rate of occurrence (e.g., incidence or odds ratio) of the adverse event(s), and FAERS data cannot be used for such a calculation.
- ☒ The serious risk of concern has a delayed time to onset, or delayed time to detection after exposure (e.g., cancer), and FAERS data are more useful for detecting events that are closely linked in time to initiation of drug therapy.
- ☐ The serious risk of concern occurs commonly in the population (e.g., myocardial infarction) and FAERS data are more useful in detecting rare serious adverse events for which the background rates are low.
- ☐ Other

[If you selected "other," expand on the reason(s) why FAERS is not sufficient.]

*Complete Q4.d when the ARIA system cannot provide the necessary data and Q4.b does not apply.*

**d. The currently available data within the ARIA system cannot be used to fully characterize the serious risk of interest because: *[Select all that apply then go to Q.4.e ]***

- ☐ Cannot identify exposure to the drug(s) of interest in the database.
- ☒ Serious risk (adverse event) of concern cannot be identified in the database.
- ☐ The population(s) of interest cannot be identified in the database.
- ☒ Long-term follow-up information required to assess the serious risk are not available in the database.
- ☒ Important confounders or covariates are not available or well represented in the database.
- ☐ The database does not contain an adequate number of exposed patients to provide sufficient statistical power to analyze the association between the drug and the serious risk of concern.
- ☐ The purpose of the evaluation is to rule out a modest relative risk, and observational studies, such as an ARIA analysis, are not well suited for such use.
- ☐ Other

[If you selected "other," expand on the reason(s) why ARIA is not sufficient.]

- e. If FAERS and the ARIA system are not sufficient for the purpose in Q1. and Q4.a, is a study sufficient?  
[Select either “Yes” or “No” and provide the appropriate responses.]

☒ Yes, a study is sufficient [Explain your answer in the textbox and then go to Q.5]

This study design permits the collection of long-term safety data and potential identification of confounders that may impact data analysis.

☐ No, a study is not sufficient [Select all explanations that apply then go to Q.4.f]

- ☐ Need to minimize bias and/or confounding via randomization
- ☐ Need for placebo control
- ☐ Need to capture detailed information about covariates or confounders that are either not routinely collected during the usual course of medical practice, or are not collected at the frequency needed for assessment of the safety issue (e.g. hourly blood glucose measures, etc.).
- ☐ Need pre-specified and prospective active data collection of the outcome/endpoint of interest
- ☐ Other

[If you selected “other,” expand on the reason(s) why a study is not sufficient.]

- f. ☐ Because a study is not sufficient, a clinical trial is required. [Go to Q.5]

5. **For all PMRs and PMCs:** What type of study or clinical trial is needed to achieve the goal described in Q1 or Q4.a above?

[Select ONE OPTION only under either “Type of Study” or “Type of clinical Trial”]

#### TYPE OF STUDY

- ☐ Drug interaction or bioavailability studies (nonclinical only)
- ☐ Epidemiologic (observational) study related to safe drug use
- ☐ Epidemiologic (observational) study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
- ☐ Immunogenicity study (nonclinical)
- ☐ Meta-analysis or pooled analysis of previous observational studies
- ☐ Nonclinical (animal) study (e.g., genotoxicity, carcinogenicity, reproductive toxicology)
- ☐ Nonclinical (in vitro) study (laboratory/microbiology resistance, receptor affinity)
- ☐ Pharmacogenetic or pharmacogenomic study
- ☐ Pharmacokinetic (PK) and/or pharmacodynamics (PD) study (nonclinical only)
- ☐ Quality CMC study (e.g., manufacturing, studies on impurities)
- ☐ Quality stability study
- ☒ Registry-based observational study

#### TYPE OF STUDY

☐ Other (describe) \_\_\_\_\_

#### TYPE OF CLINICAL TRIAL

- ☐ Combined PK/PD, safety and/or efficacy trial (*PREA\* PMRs only*)
- ☐ Dose-response clinical trial
- ☐ Dosing trial (e.g., alternative dosing schedule)
- ☐ Drug interaction or bioavailability clinical trial (clinical only)
- ☐ Immunogenicity trial (clinical)
- ☐ Meta-analysis or pooled analysis of previous clinical trials
- ☐ Pharmacogenetic or pharmacogenomic clinical trial
- ☐ Pharmacokinetic (PK) and/or pharmacodynamic (PD) clinical trial
- ☐ Primary efficacy clinical trial (i.e., with a primary efficacy endpoint; to further define efficacy; may include secondary safety endpoints)
- ☐ Primary safety clinical trial (e.g., to evaluate the long-term safety of a drug; to evaluate drug toxicity in a subpopulation; may include secondary efficacy endpoints) – *excludes SOT*
- ☐ Safety outcomes trial (SOT)\*\*
- ☐ Thorough Q-T clinical trial
- ☐ Other (describe) \_\_\_\_\_

\* Note that under PREA, clinical trials involving pediatric patients are specifically referred to as “studies.” However, for the purposes of this template, PREA investigations are categorized according to the established definitions of “studies” and “trials” (see Footnotes 3 and 4).

\*\* A safety outcomes trial (SOT) is defined as a large, prospective, randomized, controlled trial that is specifically designed and adequately powered to test a safety hypothesis using a clinical outcome, generally irreversible morbidity or mortality, as the primary trial endpoint. A cardiovascular outcomes trial (CVOT) is an example of an SOT.

#### SECTION D: PMR/PMC Additional Information

1. This PMR/PMC applies to other drugs or applications (e.g. drugs in a therapeutic class; different formulations of the same drug).

- ☐ Yes  
☒ No



**2. This study or clinical trial focuses on the following special population(s) or circumstance(s):**

*[Select all that apply]*

- ☐ For non-PREA pediatric studies/trials only: Pediatric population
- ☐ Geriatric population
- ☐ Lactating/nursing mothers
- ☐ Medical Countermeasures (e.g. anthrax exposure, bioterrorism)
- ☐ Orphan or rare disease population
- ☐ Pregnant women
- ☐ Racial/ethnic population
- ☒ Not applicable

**3. (Complete if applicable) Additional comments about the PMR/PMC** (e.g., points or concerns not previously described; explanation for inclusion of milestones other than the 3 “core” milestones or draft protocol submission)

---

**SECTION E: PMR/PMC Development Coordinator Statements**<sup>8</sup>[Error! Reference source not found.](#)

**1. The PMR/PMC is clear, feasible, and appropriate<sup>9</sup> because:** *[Select all that apply]*

- ☒ The study/clinical trial meets criteria for a PMR or a PMC.
- ☒ The objectives of the study/clinical trial are clear from the description of the PMR/PMC.
- ☐ The applicant has adequately justified the choice of milestone dates.
- ☐ The applicant has had sufficient time to review the PMR/PMC, ask questions, determine feasibility, and contribute to the development process.

**2. ☐ (If the PMR/PMC is a randomized controlled clinical trial) The following ethical considerations were made with regard to:**

- There is a significant question about the public health risks of the drug.
- There is not enough existing information to assess the public health risks of the drug.
- Information about the public health risks cannot be gained through a different kind of investigation.
- The trial will be appropriately designed to answer question about a drug’s efficacy or safety.

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<sup>8</sup> This section is completed by the PMR/PMC Development Coordinator, who is usually the OND division’s Deputy Director for Safety (DDS). See DEFINITIONS section of CDER MAPP 6010.9, *Procedures and Responsibilities for Developing Postmarketing Requirements and Commitments*.

<sup>9</sup> See POLICY section of CDER MAPP 6010.9.

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

3. ☒ **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.**

Insert electronic signature (usually the Deputy Director for Safety)

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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.**  
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/s/  
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DAWN WILLIAMS  
03/20/2018

TATIANA OUSSOVA  
03/21/2018



**Department of Health and Human Services  
Food and Drug Administration  
Center for Drug Evaluation and Research | Office of Surveillance and Epidemiology (OSE)**

**Epidemiology: ARIA Sufficiency Memo  
Version: 2018-01-24**

Date:	March 16, 2018
Reviewer/ Team Leader:	Patricia Bright, PhD, MSPH Division of Epidemiology I
Deputy Division Director:	Sukhminder K. Sandhu, PhD, MPH, MS Division of Epidemiology I
Subject:	Active Risk Identification and Assessment (ARIA) Sufficiency Memo for Pregnancy Safety Concerns
Drug Name:	Tilrakizumab
Application Type/#:	BLA 761067
Applicant/Sponsor:	Merck Sharp & Dohme Corp.
OSE RCM #:	2017-1627

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## Expedited ARIA Sufficiency Template for Pregnancy Safety Concerns

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### 1. BACKGROUND INFORMATION

#### 1.1. Medical Product

Psoriasis is a chronic inflammatory skin disease which may undergo intermittent improvements and relapses in susceptible individuals over the course of their lifetime. Although traditional systemic therapies for psoriasis are effective, there may be a loss of efficacy during long-term use or patients may experience adverse events related to specific treatments.

Tildrakizumab, a subcutaneous (SC) biologic agent, is proposed for the treatment of moderate-to-severe plaque psoriasis. Tildrakizumab is a high affinity (297 pM) humanized immunoglobulin G1/kappa (IgG1/κ) monoclonal antibody that binds to IL-23/P19 subunit and blocks the interaction of human IL-23 with the IL-23 receptor [1]. IL-23, a naturally occurring cytokine, is involved in inflammatory and immune responses. Tildrakizumab inhibits the release of proinflammatory cytokines and chemokines.

Potential risks associated with immunomodulators used for psoriasis treatment include infection, malignancy, hypersensitivity reactions, injection site reactions and MACE [1].

#### 1.2. Describe the Safety Concern – Pregnancy Risk

The Division of Pediatric and Maternal Health (DPMH) labeling review [2] for the Pregnancy and Lactation Labeling Rule (PLLR) stated the following:

##### “Review of Literature

DPMH searched PubMed, Embase, ReproTox and TERIS databases for information regarding Ilumya (tildrakizumab) injection and use during pregnancy. No published information was identified. As per the applicant, no studies of Ilumya injection have been conducted in pregnant women.

##### Review of Clinical Trials

Because the drug has not yet been approved, no pharmacovigilance database has been established. Across the Ilumya for injection clinical development program, female subjects who were pregnant or lactating were excluded from enrollment in the clinical trials. However, 12 exposures during pregnancy with known outcomes and one pregnancy with an outcome pending have occurred across the clinical development program. Pregnancy outcomes included 6 cases of fetal loss (2 early spontaneous abortions occurring at 4 and 8 weeks of gestation in women exposed to Ilumya 200 mg and 4 elective abortions for personal reasons- no malformations were detected) and 6 full term normal live births; 1 pregnancy outcome is pending.

These limited clinical data are insufficient to draw meaningful safety conclusions about the effects of Ilumya during pregnancy and lactation.”



### 1.3. FDAAA Purpose (per Section 505(o)(3)(B))

Purpose	
Assess a known serious risk	
Assess signals of serious risk	
Identify unexpected serious risk when available data indicate potential for serious risk	X

## 2. REVIEW QUESTIONS

### 2.1. Why is pregnancy safety a safety concern for this product? Check all that apply.

- ☐ Specific FDA-approved indication in pregnant women exists and exposure is expected
- ☐ No approved indication, but practitioners may use product off-label in pregnant women
- ☒ No approved indication, but there is the potential for inadvertent exposure before a pregnancy is recognized
- ☒ No approved indication, but use in women of child bearing age is a general concern

### 2.2. Regulatory Goal

- ☒ *Signal detection* – Nonspecific safety concern with no prerequisite level of statistical precision and certainty
- ☐ *Signal refinement of specific outcome(s)* – Important safety concern needing moderate level of statistical precision and certainty.
- ☐ *Signal evaluation of specific outcome(s)* – Important safety concern needing highest level of statistical precision and certainty (e.g., chart review).

### 2.3. What type of analysis or study design is being considered or requested along with ARIA? Check all that apply.

- ☒ Pregnancy registry with internal comparison group
- ☐ Pregnancy registry with external comparison group
- ☐ Enhanced pharmacovigilance (i.e., passive surveillance enhanced by with additional actions)
- ☐ Electronic database study with chart review
- ☒ Electronic database study without chart review
- ☐ Other, please specify:

### 2.4. Which are the major areas where ARIA not sufficient, and what would be needed to make ARIA sufficient?

- ☒ Study Population
- ☐ Exposures
- ☒ Outcomes
- ☐ Covariates
- ☒ Analytical Tools



For any checked boxes above, please describe briefly:

Study Population and Outcomes: ARIA is insufficient to identify the study population (babies that experienced in utero exposure or postpartum exposure through lactation) because the mother and baby records are not currently linked in Sentinel. Thus, the exposure corresponding to the mother and potential outcomes corresponding to the infant cannot be connected. This lack of linkage between mother and baby records renders ARIA insufficient for both the study population and outcome identification.

Analytical Tools: ARIA analytic tools are not sufficient to assess the regulatory question of interest because data mining methods have not been tested for birth defects and other pregnancy outcomes.

We did not formally assess the other parameters given that the mother-infant linkage is not currently available in ARIA.

## 2.5. Please include the proposed PMR language in the approval letter.

The following language (still in draft form) has been proposed for PMRs related to pregnancy outcomes:

*A prospective, registry based observational exposure cohort study that compares the maternal, fetal, and infant outcomes of women exposed to tildrakizumab during pregnancy to an unexposed control population. The registry will detect and record major and minor congenital malformations, spontaneous abortions, stillbirths, elective terminations, small for gestational age, and any other adverse pregnancy outcomes. These outcomes will be assessed throughout pregnancy. Infant outcomes, including neonatal deaths, infections in the first 6 months of life, and effects on postnatal growth and development, will be assessed through at least the first year of life.*

*And*

*An additional study that uses a different study design (for example a retrospective cohort study using claims or electronic medical record data or a case control study) to assess major congenital malformations, spontaneous abortions, stillbirths, small for gestational age, neonatal deaths, and infant infections in women exposed to guselkumab during pregnancy compared to an unexposed control population.*

The finalized PMR language will be issued upon approval.



**U.S. FOOD & DRUG**  
ADMINISTRATION

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<sup>1</sup> Sponsor Original Submission, GlobalSubmit Review: Upload dated March 23, 2017, Tildrakizumab, Clinical Overview.

<sup>2</sup> Mastroyannis, Christos, Division of Pediatric and Maternal Health, Pregnancy and Lactation Labeling Rule (PLLR) Labeling Review, BLA 761067, dated December 21, 2017, Reference ID: 4198754.



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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.**  
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/s/  
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PATRICIA L BRIGHT  
03/16/2018

SUKHMINDER K SANDHU  
03/16/2018

JUDITH W ZANDER  
03/20/2018

MICHAEL D NGUYEN  
03/20/2018

ROBERT BALL  
03/20/2018

**PMR/PMC DEVELOPMENT TEMPLATE**  
For 506B Reportable<sup>1</sup> PMRs and PMCs only


This form describes and provides the rationale for postmarketing requirements/commitments (PMRs/PMCs) subject to reporting requirements under section 506B of the FDCA.

Complete this form using the [instructions](#) (see Appendix A) and by referring to [MAPP 6010.9](#), “Procedures and Responsibilities for Developing Postmarketing Commitments and Requirements.”

**Note:** Do *not* use this template for CMC PMCs. Instead, use the CMC PMC Development Template.<sup>1</sup>

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**SECTION A: Administrative Information**

NDA/BLA/Supplement # 761067  
PMR/PMC Set (####-#)   
Product Name: Ilumya™ (tildrakizumab) injection, for subcutaneous use  
Applicant Name: Merck Sharp & Dohme Corporation  
ODE/Division: ODE 3/DDDP

**SECTION B: PMR/PMC Information**

**1. PMR/PMC Description**

A prospective, registry based observational exposure cohort study that compares the maternal, fetal, and infant outcomes of women exposed to tildrakizumab during pregnancy to an unexposed control population. The registry will detect and record major and minor congenital malformations, spontaneous abortions, stillbirths, elective terminations, small for gestational age, and any other adverse pregnancy outcomes. These outcomes will be assessed throughout pregnancy. Infant outcomes, including neonatal deaths, infections in the first 6 months of life, and effects on postnatal growth and development, will be assessed through at least the first year of life.

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**2. PMR/PMC Schedule Milestones<sup>2, 3</sup>**

Draft Protocol Submission: 01/2019  
Final Protocol Submission: 06/2019  
Study/Trial Completion: 01/2029  
Interim /Other:  
Final Report Submission: 01/2030

---

<sup>1</sup> 506B “reportable” includes all studies/trials an applicant has agreed upon or is required to conduct related to clinical safety, clinical efficacy, clinical pharmacology, or nonclinical toxicology (21 CFR 314.81(b)(2)(vii) and 21 CFR 601.70(a)). All PMRs are considered 506 “reportable.” A separate development template is used for 506 B non-reportable (e.g., chemistry, manufacturing, and controls (CMC)) PMCs, which is located in the CST.

<sup>2</sup> Final protocol, study/trial completion, and final report submissions are required milestones. Draft protocol submissions and interim milestones are optional. EXCEPTION: PMRs/PMCs for medical countermeasures may have only draft/final protocol submission dates and no other milestones, since the study/trial will only be initiated in the event of an emergency. Interim milestones may include interim report milestones for studies/trials that may be of long duration. May include interim subject accrual milestone (e.g., for accelerated approval PMRs). Other milestones should be justified in Section D, question 3.

<sup>3</sup> Dates should be numerical (e.g., 05/2016). PREA PMR date format may be MM/DD/YYYY if a day is specified.

## **SECTION C: PMR/PMC Rationale**

### **1. Describe the particular review issue and the goal of the study<sup>4</sup> or clinical trial<sup>5</sup> in the text box below.**

Moderate to severe psoriasis occurs in women of child bearing age. Therefore, we expect that there will be some exposure of pregnant women to tildrakizumab. Pregnant women were excluded from the development program and data is needed in this population.

### **2. Explain why this issue can be evaluated post-approval and does not need to be addressed prior to approval. (Select one explanation below.)**

- ☐ Subpart I or H (animal efficacy rule) PMR: Approved under Subpart I or H (animal efficacy rule) authorities; postmarketing study/trial required to verify and describe clinical benefit [\[Skip to Q.5\]](#)
- ☐ Subpart H or E (accelerated approval) PMR: Approved under Subpart H or E (accelerated approval) authorities; postmarketing study/trial required to verify and describe clinical benefit [\[Skip to Q.5\]](#)
- ☐ PREA PMR: Meets PREA postmarketing pediatric study *requirements* [\[Skip to Q.5\]](#)
- ☒ FDAAA PMR (safety): Benefit/risk profile of the drug appears favorable; however, there are uncertainties about aspects of the drug's safety profile. Because the investigation will evaluate a serious risk, it meets FDAAA requirements for a postmarketing safety study or trial [\[Go to Q.3\]](#)
- ☐ PMC (506B reportable): Benefit/risk profile of the drug appears favorable; however, there are uncertainties about aspects of the drug's efficacy profile or other issues. The purpose of the investigation does not meet requirements under Subpart I/H , H/E, PREA, or FDAAA to be a PMR, and therefore the investigation is a PMC. [\[Go to Q.3\]](#)

### **3. For FDAAA PMRs and 506B PMCs only**

**The study or trial can be conducted post-approval because:** [\[Select all that apply\]](#)

- ☐ Longer-term data needed to further characterize the safety/efficacy of the drug
- ☐ Based on the purpose and/or design, it is only feasible to conduct the study/trial post-approval
- ☒ Prior clinical experience (e.g., with other drugs in the class) indicates adequate safety or efficacy data to support approval, but some uncertainties about safety or efficacy remain and should be further characterized
- ☒ Only a small subpopulation is affected (e.g., patients with severe renal impairment) and effects of the drug in the subpopulation can be further evaluated after approval
- ☐ Study/trial is to further explore a theoretical concern that does not impact the approval determination
- ☐ Other reason (describe in text box below)

[If you selected "other reason," expand on the reason(s) why it is appropriate to conduct the study/trial postapproval and why the issue does not need to be addressed *prior to approval*.]

<sup>4</sup> A "study" is an investigation that is not a clinical trial, such as an observational (epidemiologic) study, animal study, or laboratory experiment.

<sup>5</sup> A "clinical trial" is any prospective investigation in which the applicant or investigator determines the method of assigning the drug product(s) or other interventions to one or more human subjects. Note that under PREA, clinical trials involving pediatric patients are specifically referred to as "studies."

4. **For FDAAA PMRs only** *[for PMCs skip to Q.5]. Complete this entire section*

a. **The purpose of the study/clinical trial is to:** *[Select one, then go to Q.4.b]*

- ☐ Assess a known serious risk related to the use of the drug
- ☐ Assess a signal 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

*Complete Q4.b if the necessary data can only be obtained through a particular type of nonclinical study or clinical pharmacology trial. Otherwise complete Q4.c and Q4.d.*

b. **FAERS<sup>6</sup> and Sentinel's postmarket ARIA<sup>7</sup> system are not sufficient for the purposes described in Q1. and Q4.a because the safety issue involves:**

*[Select all that apply then to skip to Q.5. If none apply, answer both Q4.c and Q4.d]*

- ☐ A serious risk of genotoxicity, carcinogenicity, or reproductive toxicity, and these signals are initially best assessed through in vitro or animal studies.
- ☐ A potential drug interaction resulting in lower/higher drug exposure and resultant serious drug risks, and accurate assessment of an interaction is feasible only through in vitro mechanistic studies or clinical pharmacokinetic and pharmacodynamics trials.
- ☐ The potential for lower/higher drug exposure and resultant serious drug risks in patients with hepatic or renal impairment, or other metabolic abnormalities, and accurate assessment is feasible only through in vitro mechanistic studies or clinical pharmacokinetic and pharmacodynamics trials.
- ☐ An immunologic concern for which accurate assessment requires in vitro development or validation of specific assays.

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<sup>6</sup> FDA Adverse Event Reporting System (FAERS)

<sup>7</sup> Active Risk Identification and Analysis (ARIA)

*Complete Q4.c when FAERS cannot provide the necessary data and Q4.b does not apply*

**c. FAERS data cannot be used to fully characterize the serious risk of interest because:**

*[Select all that apply then go to Q.4.d ]*

- ☒ Assessment of the serious risk necessitates calculation of the rate of occurrence (e.g., incidence or odds ratio) of the adverse event(s), and FAERS data cannot be used for such a calculation.
- ☐ The serious risk of concern has a delayed time to onset, or delayed time to detection after exposure (e.g., cancer), and FAERS data are more useful for detecting events that are closely linked in time to initiation of drug therapy.
- ☐ The serious risk of concern occurs commonly in the population (e.g., myocardial infarction) and FAERS data are more useful in detecting rare serious adverse events for which the background rates are low.
- ☐ Other

[If you selected "other," expand on the reason(s) why FAERS is not sufficient.]

*Complete Q4.d when the ARIA system cannot provide the necessary data and Q4.b does not apply.*

**d. The currently available data within the ARIA system cannot be used to fully characterize the serious risk of interest because:** *[Select all that apply then go to Q.4.e ]*

- ☐ Cannot identify exposure to the drug(s) of interest in the database.
- ☐ Serious risk (adverse event) of concern cannot be identified in the database.
- ☒ The population(s) of interest cannot be identified in the database.
- ☒ Long-term follow-up information required to assess the serious risk are not available in the database.
- ☒ Important confounders or covariates are not available or well represented in the database.
- ☐ The database does not contain an adequate number of exposed patients to provide sufficient statistical power to analyze the association between the drug and the serious risk of concern.
- ☐ The purpose of the evaluation is to rule out a modest relative risk, and observational studies, such as an ARIA analysis, are not well suited for such use.
- ☐ Other

[If you selected "other," expand on the reason(s) why ARIA is not sufficient.]

- e. If FAERS and the ARIA system are not sufficient for the purpose in Q1. and Q4.a, is a study sufficient?  
[Select either “Yes” or “No” and provide the appropriate responses.]

☒ Yes, a study is sufficient [Explain your answer in the textbox and then go to Q.5]

A study is sufficient to address the question of the safety of exposure to tildrakizumab during pregnancy because the population of interest can be identified, long-term follow-up information which is required to assess the serious risk can be obtained and important confounders or covariates can be determined.

☐ No, a study is not sufficient [Select all explanations that apply then go to Q.4.f]

- ☐ Need to minimize bias and/or confounding via randomization
- ☐ Need for placebo control
- ☐ Need to capture detailed information about covariates or confounders that are either not routinely collected during the usual course of medical practice, or are not collected at the frequency needed for assessment of the safety issue (e.g. hourly blood glucose measures, etc.).
- ☐ Need pre-specified and prospective active data collection of the outcome/endpoint of interest
- ☐ Other

- f. ☐ Because a study is not sufficient, a clinical trial is required. [Go to Q.5]

5. **For all PMRs and PMCs:** What type of study or clinical trial is needed to achieve the goal described in Q1 or Q4.a above?

[Select ONE OPTION only under either “Type of Study” or “Type of clinical Trial”]

**TYPE OF STUDY**

- ☐ Drug interaction or bioavailability studies (nonclinical only)
- ☐ Epidemiologic (observational) study related to safe drug use
- ☐ Epidemiologic (observational) study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
- ☐ Immunogenicity study (nonclinical)
- ☐ Meta-analysis or pooled analysis of previous observational studies
- ☐ Nonclinical (animal) study (e.g., genotoxicity, carcinogenicity, reproductive toxicology)
- ☐ Nonclinical (in vitro) study (laboratory/microbiology resistance, receptor affinity)
- ☐ Pharmacogenetic or pharmacogenomic study
- ☐ Pharmacokinetic (PK) and/or pharmacodynamics (PD) study (nonclinical only)
- ☐ Quality CMC study (e.g., manufacturing, studies on impurities)
- ☐ Quality stability study

#### TYPE OF STUDY

- ☒ Registry-based observational study  
☐ Other (describe) \_\_\_\_\_

#### TYPE OF CLINICAL TRIAL

- ☐ Combined PK/PD, safety and/or efficacy trial (*PREA\* PMRs only*)  
☐ Dose-response clinical trial  
☐ Dosing trial (e.g., alternative dosing schedule)  
☐ Drug interaction or bioavailability clinical trial (clinical only)  
☐ Immunogenicity trial (clinical)  
☐ Meta-analysis or pooled analysis of previous clinical trials  
☐ Pharmacogenetic or pharmacogenomic clinical trial  
☐ Pharmacokinetic (PK) and/or pharmacodynamic (PD) clinical trial  
☐ Primary efficacy clinical trial (i.e., with a primary efficacy endpoint; to further define efficacy; may include secondary safety endpoints)  
☐ Primary safety clinical trial (e.g., to evaluate the long-term safety of a drug; to evaluate drug toxicity in a subpopulation; may include secondary efficacy endpoints) – *excludes SOT*  
☐ Safety outcomes trial (SOT)\*\*  
☐ Thorough Q-T clinical trial  
☐ Other (describe) \_\_\_\_\_

\* Note that under PREA, clinical trials involving pediatric patients are specifically referred to as “studies.” However, for the purposes of this template, PREA investigations are categorized according to the established definitions of “studies” and “trials” (see Footnotes 3 and 4).

\*\* A safety outcomes trial (SOT) is defined as a large, prospective, randomized, controlled trial that is specifically designed and adequately powered to test a safety hypothesis using a clinical outcome, generally irreversible morbidity or mortality, as the primary trial endpoint. A cardiovascular outcomes trial (CVOT) is an example of an SOT.

#### SECTION D: PMR/PMC Additional Information

1. This PMR/PMC applies to other drugs or applications (e.g. drugs in a therapeutic class; different formulations of the same drug).

- ☐ Yes  
☒ No



**2. This study or clinical trial focuses on the following special population(s) or circumstance(s):**

*[Select all that apply]*

- ☐ For *non-PREA* pediatric studies/trials only: Pediatric population
- ☐ Geriatric population
- ☐ Lactating/nursing mothers
- ☐ Medical Countermeasures (e.g. anthrax exposure, bioterrorism)
- ☐ Orphan or rare disease population
- ☒ Pregnant women
- ☐ Racial/ethnic population
- ☐ Not applicable

**3. (Complete if applicable) Additional comments about the PMR/PMC** (e.g., points or concerns not previously described; explanation for inclusion of milestones other than the 3 “core” milestones or draft protocol submission)

---

**SECTION E: PMR/PMC Development Coordinator Statements<sup>8</sup>**

**1. The PMR/PMC is clear, feasible, and appropriate<sup>9</sup> because:** *[Select all that apply]*

- ☒ The study/clinical trial meets criteria for a PMR or a PMC.
- ☒ The objectives of the study/clinical trial are clear from the description of the PMR/PMC.
- ☐ The applicant has adequately justified the choice of milestone dates.
- ☐ The applicant has had sufficient time to review the PMR/PMC, ask questions, determine feasibility, and contribute to the development process.

**2. ☐ (If the PMR/PMC is a randomized controlled clinical trial) The following ethical considerations were made with regard to:**

- There is a significant question about the public health risks of the drug.
- There is not enough existing information to assess the public health risks of the drug.
- Information about the public health risks cannot be gained through a different kind of investigation.
- The trial will be appropriately designed to answer question about a drug’s efficacy or safety.

---

<sup>8</sup> This section is completed by the PMR/PMC Development Coordinator, who is usually the OND division’s Deputy Director for Safety (DDS). See DEFINITIONS section of CDER MAPP 6010.9, *Procedures and Responsibilities for Developing Postmarketing Requirements and Commitments*.

<sup>9</sup> See POLICY section of CDER MAPP 6010.9.



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

3. ☒ **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.**

Insert electronic signature (usually the Deputy Director for Safety)

## Appendix A

### PMR/PMC Development Template (FRM-ADMIN-60)

#### Instructions for Use

[click [here](#) to return to the template]

#### ***Purpose:***

The PMR/PMC Development template (thereafter, template) is a review tool to help the team decide that PMRs/PMCs are needed, articulate the rationale for the PMRs/PMCs, obtain initial supervisory concurrence, and to inform discussions with the applicant.

#### ***Who completes this template:***

The **PMR/PMC Development Coordinator** (usually the OND division's Deputy Director for Safety) may delegate the initial draft (i.e., filling out) of the template to an **assigned reviewer**. However, the PMR/PMC Development Coordinator is responsible for ensuring the accuracy and completeness of the template and for signing off on the template.

#### ***How to complete this template:***

The assigned reviewer and PMR/PMC Development Coordinator should complete the template by following the *Instructions For Use*. The PMR/PMC Development Coordinator will review each PMR/PMC to ensure it is clearly written, has an appropriate rationale, and that milestones were appropriately selected to result in timely submission of appropriate data to address the issue that prompted the PMR/PMC.

A separate template is completed for **each** individual PMR and 506B “reportable” PMC.<sup>10</sup> The separate templates are then combined into one document for archiving (see “How to archive the completed template”).

A draft template should be completed by the date targeted to begin PMR/PMC discussions with the applicant, as documented in the Filing Letter. Once concurrence on the PMR/PMC is reached with the applicant, the draft language in the template can be finalized.

#### ***How to archive the completed template:***

The OND division's Safety Regulatory Project Manager should ensure appropriate sign-off on the completed template, as determined by the division, and that the process below is followed to ensure the completed template is filed correctly.

Completed templates for all PMRs and 506B “reportable” PMCs for a specific application should be combined and filed in CDER's electronic archival system as a single document.<sup>11</sup> This single document should be filed as *PMR/PMC Development Template* before filing the action letter that establishes the PMR(s)/PMC(s).

For (s)NDA/(s)BLA submissions, the completed, signed template should be included in the Action Package.

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<sup>10</sup> 506B “reportable” includes all studies/trials an applicant has agreed upon or is required to conduct related to clinical safety, clinical efficacy, clinical pharmacology, or nonclinical toxicology (21 CFR 314.81(b)(2)(vii) and 21 CFR 601.70(a)). All PMRs are considered 506 “reportable.” A separate development template is used for 506 B *non-reportable* (e.g., chemistry, manufacturing, and controls (CMC)) PMCs.

<sup>11</sup> A single document facilitates data entry by the document room by preventing the need to upload and archive multiple templates.

---

## Instructions:

### **SECTION A: Administrative Information** [Click [here](#) to return to Section A of the template]

Complete each field in section A. Do not leave any fields blank.

### **SECTION B: PMR/PMC Information** [Click [here](#) to return to Section B of the template]

- 1. PMR/PMC Description:** In the textbox, enter the wording for the PMR/PMC that will go in the letter notifying the applicant of the PMR/PMC (e.g., NDA action letter) and will also display in the FDA's PMR/PMC database. The PMR/PMC description should be written clearly enough to result in the applicant's timely submission of the appropriate data to address the issue that prompted the postmarketing study or clinical trial.

PMR/PMC descriptions are specific to the drug, indication, and issues under evaluation. Nevertheless, PMR/PMC descriptions should generally reflect the design of the clinical trial or study (e.g. randomized, double-blind, active control trial; registry based prospective cohort study), the population(s) to be studied, the exposure or intervention of interest, a comparator group (if applicable), and the study/trial goals and objectives.<sup>12</sup>

Avoid limiting the PMR/PMC description to a citation of the name of a specific study or clinical trial that may be ongoing (e.g., "Complete trial ABC123, *A Randomized, Placebo-Controlled Efficacy Trial of DRUG against COMPARATOR*"). The study/trial name may be included, but in addition, the PMR/PMC description should describe the design features of the study or clinical trial. In this way, should unforeseen developments preclude completion of the named study/trial, the PMR/PMC description provides sufficient information for FDA, the applicant, and the public to determine the type of study/trial that would be considered sufficient to fulfill the PMR/PMC.

Certain types of studies and clinical trials are commonly issued as PMRs/PMCs (e.g., drug-drug interaction trials; hepatic impairment PK trials). For these, a 'standard' PMR/PMC description may be employed [\[see Appendix B for examples\]](#).

- 2. PMR/PMC Milestones:** List the PMR/PMC milestones in the specified format.

Dates should be specified for all milestones. The milestone date format should be MM/YYYY; however, the milestone date format for PREA PMRs may be MM/DD/YYYY if a day is specified.

The Final Protocol Submission, Study/Trial Completion, and Final Report Submission milestones are considered "core" PMR/PMC milestones. These are included in every PMR/PMC schedule unless they are not applicable (e.g., study/trial is ongoing; the PMR is for a medical countermeasure study/trial that will not be initiated unless there is an emergency).

The Draft Protocol Submission milestone may be included to ensure sufficient time for FDA review and comment on the protocol before it is finalized.<sup>13</sup>

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<sup>12</sup> The PMR/PMC description may also include primary and important secondary endpoints, as relevant. Typically the PMR/PMC description should not include description of milestones or other indicators of study/trial progress (e.g., frequency of interim reports), as these are described in the PMR/PMC timetable. .

<sup>13</sup> "Final" implies that the applicant has submitted a protocol, the FDA review team has sent comments to the applicant, and the protocol has been revised as needed to meet the goal of the study or clinical trial. Thus, the date for this milestone should be selected to allow for the discussion period

“Other” milestones may include interim or annual report submission or subject accrual milestones.

Typically, submission of revised labeling (to reflect results from completed studies/trials are **not** included as PMR/PMC milestones.<sup>14</sup>

## **SECTION C: PMR/PMC Rationale** [Click [here](#) to return to Section C of the template]

### **1. Describe the review issue and the goal of the study or clinical trial.**

This section should summarize the **rationale** for the study/trial. The section should not repeat the description of the PMR/PMC provided in Section B.

The summary should briefly identify the review issue (safety signal for FDAAA PMRs; efficacy or other question for non-FDAAA PMRs), cite the source of the data if it includes information external to the application, and explain the intent of the study/trial and why we think the results of the PMR/PMC will be important.

The intent of the study/trial is the explanation of what it is that FDA wants to know. Intents include, but are not limited to:

- Signal detection (e.g., detecting potential serious risks associated with the drug)
- Signal refinement (e.g., checking to determine whether an identified safety signal persists; conducting surveillance to obtain additional follow-up on a known serious risk)
- Signal evaluation (e.g., obtaining a precise estimate of the serious risk associated with a drug)

Examples of a PMR/PMC rationale:

*DRUG-X is metabolized through CYPYYYY, which can be inhibited by COMMONDRUGZ. This DDI trial will evaluate whether DRUGX levels are sufficiently increased to warrant a dose reduction when used concurrently with COMMONDRUGZ, to reduce the severity and/or likelihood of serious adverse effects caused by DRUGX.*

*DRUG-Y is intended for chronic use in patients with CONDITIONA. During clinical development of DRUG-Y, the maximum duration of patient exposure was 6 months. This long-term efficacy trial will evaluate whether positive treatment effects are maintained when exposures exceed 6 months.*

### **2. Explain why this issue can be evaluated post-approval and does not need to be addressed prior to approval.**

This section documents the statutory or regulatory authorities that *necessitate* that the study or clinical trial be done post-approval (e.g., confirmatory trials for accelerated approval), **or** why the issue does not preclude an approval action and can be evaluated after approval without compromising safety and efficacy considerations.

Only one option should be selected.

### **3. For FDAAA PMRs and 506B PMCs only**

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needed to create a well-designed study or clinical trial. See FDA guidance for industry, [Postmarketing Studies and Clinical Trials — Implementation of Section 505\(o\)\(3\) of the Federal Food, Drug, and Cosmetic Act](#).

<sup>14</sup> Exceptions are PREA and Accelerated Approval PMRs, since those authorities necessitate submission of revised labeling to reflect PMR results.

This section expands on the reasons why the FDAAA PMR or 506B PMC can be conducted post-approval and do not need to be addressed prior to approval.

This section applies only to FDAAA PMRs and 506B “reportable” PMCs because the statutory and regulatory basis is sufficient explanation for all other PMRs (i.e., PREA, accelerated approval, and animal rule PMRs).

#### 4. For FDAAA PMRs only

This section summarizes the statutory purpose of the FDAAA PMRs, the reasons why FAERS<sup>15</sup> and Sentinel’s ARIA<sup>16</sup> system are insufficient for this purpose and, as applicable, why a study is insufficient for this purpose and a clinical trial is necessary. FDA must make each of these hierarchical determinations before requiring a FDAAA PMR.

##### **Question 4.a: identify the purpose of the study/clinical trial:**

As mandated by Section 505(o)(3)(A), postmarketing studies and clinical trials may be required for the three purposes listed below. Therefore to document the rationale for requiring a FDAAA PMR, you must identify one of the following:

- To assess a known serious risk related to the use of the drug
- To assess signals of serious risk related to the use of the drug
- To identify an unexpected serious risk when available data indicates the potential for a serious risk

##### **Questions 4.b-d: Explanation of whether FAERS and Sentinel’s postmarket ARIA system are sufficient for the purposes described in Q1. and Q4.a.**

Studies/trials are required as FDAAA PMRs when FAERS and the ARIA system are determined to be insufficient to assess the safety issue. Responses to questions 4.b-d briefly summarize the reasons why FAERS and the ARIA system have been determined insufficient.

The explanation of why FAERS is insufficient to further characterize the serious risk(s) of concern should be informed by the FDA draft guidance, *Postmarketing Studies and Clinical Trials — Implementation of Section 505(o)(3) of the Federal Food, Drug, and Cosmetic Act* and by discussions with the Division of Pharmacovigilance (DPV) in the Office of Surveillance and Epidemiology (OSE).

The explanation of why the ARIA system is insufficient to further characterize the serious risk(s) of concern should be informed by discussions with the Division of Epidemiology (DEPI) in OSE, the DEPI *ARIA Sufficiency Memorandum*, and the aforementioned FDA guidance. It is acceptable to excerpt text from the *ARIA Sufficiency Memorandum*.

##### **Question Q4.e: Determination of whether a study is sufficient for the purposes described in Q1. and Q4.a.**

The explanation of why a study is (or is not) sufficient to further characterize the serious risk(s) of concern should be informed by the nature of the study (e.g., an animal study is the generally accepted standard for assessment of genotoxicity) and relevant discussions with other scientific disciplines such as Clinical Pharmacology, Pharmacology/Toxicology, and DEPI.

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<sup>15</sup> FDA Adverse Event Reporting System (FAERS)

<sup>16</sup> Active Risk Identification and Analysis (ARIA)

Examples of situations when an *observational* study may not be sufficient, and a clinical trial required, include (but are not limited to):

- Need to minimize bias and/or confounding via randomization
- Need for placebo control
- Need to capture detailed information about covariates or confounders that are either not routinely collected during the usual course of medical practice, or not collected at the frequency needed for assessment of the safety issue (e.g. hourly blood glucose measures, etc.).
- Need pre-specified and prospective active data collection of outcome(s)/endpoint(s)

***Question Q4.f: Conclusion that only a clinical trial is sufficient for the purposes described in Q1. and Q4.a.***

Under FDAAA, when FAERS, the ARIA system, and a study are considered insufficient, then a clinical trial is necessary for the specified purposes.

**5. For all PMRs and PMCs: What type of study or clinical trial is needed to achieve the goal?**

This section should be completed for all PMRs and PMCs.

Select the best summary description of the type of postmarketing study or clinical trial. Select only **ONE** option under either “type of study” or “type of clinical trial.” Do not choose a option under both categories.

**SECTION D: PMR/PMC Additional information** [Click [here](#) to return to Section D of the template]

This section provides additional information about the PMRs and PMCs.

**1. Does this PMR/PMC apply to other drugs (e.g. drugs in a therapeutic class)?**

Select “yes” if the PMR/PMC will apply to other drugs in the same therapeutic class or different formulations of the same drug.

**2. This study or clinical trial focuses on the following special population or circumstances:**

Select the appropriate box(es) if the study or trial focuses on a special population. If not, select “not applicable.”

**3. (Complete if applicable) Additional comments about the PMR/PMC.**

Complete this text box only if there are additional comments to add about this PMR or PMC (e.g., points or concerns not previously described; explanation for inclusion of additional milestones besides the 3 “core” milestones).

Note: Additional milestones also must be tracked by the division (see [MAPP 6010.2](#), *Responsibilities for Tracking and Communicating the Status of Postmarketing Requirements and Commitments*).

If nothing additional to add, leave text box blank.

**SECTION E: PMR/PMC Development Coordinator Statements** [Click [here](#) to return to Section E of the template]

This section is completed only by the the PMR/PMC Development Coordinator (usually the OND division’s Deputy Director for Safety) who will sign off on the completed Development Template.

**1. The PMR/PMC is clear, feasible, and appropriate because (select all that apply):**

Select the considerations FDA made to determine that the study or clinical trial is feasible to conduct, appropriately described, and informed by discussions with the applicant.

**2. The following ethical considerations were made with regard to randomized, controlled, clinical trials:**

This section is only completed if the PMR/PMC is for a randomized, controlled, clinical trial, including a clinical pharmacology trial.

It is necessary to provide this information in order to demonstrate that the relevant ethical considerations have been made regarding the trial, as recommended to FDA in the Institute of Medicine's *Ethical and Scientific Issues in Studying the Safety of Approved Drugs*.

**3. This PMR/PMC has been reviewed for clarity and consistency... reliability of drug quality.**

This attestation is to document that the necessary considerations have been made regarding the need for and appropriateness of the postmarketing study or clinical trial.

## APPENDIX B

### Examples of Standard Descriptions for Certain Clinical Pharmacology PMRs and PMCs

#### 1. Examples of standard language for Clinical Pharmacology PMRs

- Renal Impairment

Conduct a clinical pharmacokinetic trial to determine an appropriate dose of **DRUG** to minimize toxicity in patients with renal impairment. Design and conduct the trial in accordance with the FDA Guidance for Industry entitled “Pharmacokinetics in Patients with Impaired Renal Function: Study Design, Data Analysis, and Impact on Dosing and Labeling.

- Hepatic Impairment

Conduct a clinical pharmacokinetic trial to determine an appropriate dose of **DRUG** to minimize toxicity in patients with hepatic impairment. Design and conduct the trial in accordance with the FDA Guidance for Industry entitled “Pharmacokinetics in Patients with Impaired Hepatic Function: Study Design, Data Analysis, and Impact on Dosing and Labeling.

- Drug-Drug Interactions-victim drug (CYP inhibitors, UGT or transporter)

Conduct a clinical pharmacokinetic trial to evaluate the effect of repeat doses of **CYP (or other enzyme/transporter) #X#** inhibitor on the single dose pharmacokinetics of **DRUG** to address the potential for excessive drug toxicity. Design and conduct the trial in accordance with the FDA Guidance for Industry entitled “Drug Interaction Studies – Study Design, Data Analysis, Implications for Dosing, and Labeling Recommendations.”

- Drug-Drug Interactions-perpetrator drug as inhibitors of CYP#X#

Conduct a clinical pharmacokinetic trial to evaluate the effect of repeat doses of **DRUG** on the single dose pharmacokinetics of **XYZ** drug (a sensitive CYP#X# substrate) to address the potential for excessive drug toxicity. Design and conduct the trial in accordance with the FDA Guidance for Industry entitled “Drug Interaction Studies – Study Design, Data Analysis, Implications for Dosing, and Labeling Recommendations.”

#### 2. Examples of standard language for Clinical Pharmacology PMCs

PMCs to assess for potential decreased drug exposure, with potential loss of efficacy.

- Drug-Drug Interactions (gastric acid reducing agents)

Conduct a clinical pharmacokinetic trial to evaluate if gastric acid reducing agents (proton pump inhibitors, H2-receptor antagonists, and antacids) alter the bioavailability of **DRUG** and to determine appropriate dosing recommendations for **DRUG** with regard to use of concomitant gastric acid reducing agents.

- Drug-Drug Interactions-Induction

Conduct a clinical pharmacokinetic trial with repeat doses of a CYP#X# inducer on the single dose pharmacokinetics of **DRUG** to assess the magnitude of decreased drug exposure and to determine appropriate dosing recommendations. Design and conduct the trial in accordance with the FDA Guidance for Industry entitled “Drug Interaction Studies – Study Design, Data Analysis, Implications for Dosing, and Labeling Recommendations.”

- Anti-Drug Antibody Responses

Conduct an assessment of binding and neutralizing anti-drug antibody (ADA) responses with a validated assay (requested in PMC **X**) capable of sensitively detecting ADA responses in the presence of **DRUG** levels that are expected to be present in the serum at the time of patient sampling. The ADA response will be evaluated in at least **### DRUG**-treated patients. The final report will include information on the level of **DRUG** in each patient's test sample at each sampling point.



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/s/  
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DAWN WILLIAMS  
03/19/2018

TATIANA OUSSOVA  
03/20/2018

**PMR/PMC DEVELOPMENT TEMPLATE**  
For 506B Reportable<sup>1</sup> PMRs and PMCs only


This form describes and provides the rationale for postmarketing requirements/commitments (PMRs/PMCs) subject to reporting requirements under section 506B of the FDCA.

Complete this form using the [instructions](#) (see Appendix A) and by referring to [MAPP 6010.9](#), “Procedures and Responsibilities for Developing Postmarketing Commitments and Requirements.”

**Note:** Do *not* use this template for CMC PMCs. Instead, use the CMC PMC Development Template.<sup>1</sup>

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**SECTION A: Administrative Information**

NDA/BLA/Supplement # 761067  
PMR/PMC Set (####-#)   
Product Name: Ilumya™ (tildrakizumab) injection, for subcutaneous use  
Applicant Name: Merck Sharp & Dohme Corporation  
ODE/Division: ODE 3/DDDP

**SECTION B: PMR/PMC Information**

**1. PMR/PMC Description**

Conduct a Pharmacokinetics (PK), Safety and Efficacy Study in pediatric subjects 6 to <18 years of age with moderate to severe psoriasis (with a duration of exposure to tildrakizumab of at least one year).

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**2. PMR/PMC Schedule Milestones<sup>2, 3</sup>**

Draft Protocol Submission: 4Q2018  
Final Protocol Submission: 2Q2019  
Study/Trial Completion: 2/2025  
Interim /Other: Final Report Submission: 10/2025

**SECTION C: PMR/PMC Rationale**

**1. Describe the particular review issue and the goal of the study<sup>4</sup> or clinical trial<sup>5</sup> in the text box below.**

Under Section 2 of the Pediatric Research Equity Act (PREA) the applicant is required to submit adequate

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<sup>1</sup> 506B “reportable” includes all studies/trials an applicant has agreed upon or is required to conduct related to clinical safety, clinical efficacy, clinical pharmacology, or nonclinical toxicology (21 CFR 314.81(b)(2)(vii) and 21 CFR 601.70(a)). All PMRs are considered 506 “reportable.” A separate development template is used for 506 B non-reportable (e.g., chemistry, manufacturing, and controls (CMC)) PMCs, which is located in the CST.

<sup>2</sup> Final protocol, study/trial completion, and final report submissions are required milestones. Draft protocol submissions and interim milestones are optional. EXCEPTION: PMRs/PMCs for medical countermeasures may have only draft/final protocol submission dates and no other milestones, since the study/trial will only be initiated in the event of an emergency. Interim milestones may include interim report milestones for studies/trials that may be of long duration. May include interim subject accrual milestone (e.g., for accelerated approval PMRs). Other milestones should be justified in Section D, question 3.

<sup>3</sup> Dates should be numerical (e.g., 05/2016). PREA PMR date format may be MM/DD/YYYY if a day is specified.

<sup>4</sup> A “study” is an investigation that is not a clinical trial, such as an observational (epidemiologic) study, animal study, or laboratory experiment.

safety and efficacy data for pediatric subjects. There is no clinical pharmacology and safety data for subjects with plaque psoriasis age 6 to < 18 years to support labeling.

**2. Explain why this issue can be evaluated post-approval and does not need to be addressed prior to approval. (Select one explanation below.)**

- ☐ Subpart I or H (animal efficacy rule) PMR: Approved under Subpart I or H (animal efficacy rule) authorities; postmarketing study/trial required to verify and describe clinical benefit [\[Skip to Q.5\]](#)
- ☐ Subpart H or E (accelerated approval) PMR: Approved under Subpart H or E (accelerated approval) authorities; postmarketing study/trial required to verify and describe clinical benefit [\[Skip to Q.5\]](#)
- ☒ PREA PMR: Meets PREA postmarketing pediatric study *requirements* [\[Skip to Q.5\]](#)
- ☐ FDAAA PMR (safety): Benefit/risk profile of the drug appears favorable; however, there are uncertainties about aspects of the drug's safety profile. Because the investigation will evaluate a serious risk, it meets FDAAA requirements for a postmarketing safety study or trial [\[Go to Q.3\]](#)
- ☐ PMC (506B reportable): Benefit/risk profile of the drug appears favorable; however, there are uncertainties about aspects of the drug's efficacy profile or other issues. The purpose of the investigation does not meet requirements under Subpart I/H , H/E, PREA, or FDAAA to be a PMR, and therefore the investigation is a PMC. [\[Go to Q.3\]](#)

**3. For FDAAA PMRs and 506B PMCs only**

**The study or trial can be conducted post-approval because:** [\[Select all that apply\]](#)

- ☐ Longer-term data needed to further characterize the safety/efficacy of the drug
- ☐ Based on the purpose and/or design, it is only feasible to conduct the study/trial post-approval
- ☐ Prior clinical experience (e.g., with other drugs in the class) indicates adequate safety or efficacy data to support approval, but some uncertainties about safety or efficacy remain and should be further characterized
- ☐ Only a small subpopulation is affected (e.g., patients with severe renal impairment) and effects of the drug in the subpopulation can be further evaluated after approval
- ☐ Study/trial is to further explore a theoretical concern that does not impact the approval determination
- ☐ Other reason (describe in text box below)

[If you selected "other reason," expand on the reason(s) why it is appropriate to conduct the study/trial postapproval and why the issue does not need to be addressed *prior to* approval.]

<sup>5</sup> A "clinical trial" is any prospective investigation in which the applicant or investigator determines the method of assigning the drug product(s) or other interventions to one or more human subjects. Note that under PREA, clinical trials involving pediatric patients are specifically referred to as "studies."

4. **For FDAAA PMRs only** *[for PMCs skip to Q.5]. Complete this entire section*

a. **The purpose of the study/clinical trial is to:** *[Select one, then go to Q.4.b]*

- ☐ Assess a known serious risk related to the use of the drug
- ☐ Assess a signal 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

*Complete Q4.b if the necessary data can only be obtained through a particular type of nonclinical study or clinical pharmacology trial. Otherwise complete Q4.c and Q4.d.*

b. **FAERS<sup>6</sup> and Sentinel's postmarket ARIA<sup>7</sup> system are not sufficient for the purposes described in Q1. and Q4.a because the safety issue involves:**

*[Select all that apply then to skip to Q.5. If none apply, answer both Q4.c and Q4.d]*

- ☐ A serious risk of genotoxicity, carcinogenicity, or reproductive toxicity, and these signals are initially best assessed through in vitro or animal studies.
- ☐ A potential drug interaction resulting in lower/higher drug exposure and resultant serious drug risks, and accurate assessment of an interaction is feasible only through in vitro mechanistic studies or clinical pharmacokinetic and pharmacodynamics trials.
- ☐ The potential for lower/higher drug exposure and resultant serious drug risks in patients with hepatic or renal impairment, or other metabolic abnormalities, and accurate assessment is feasible only through in vitro mechanistic studies or clinical pharmacokinetic and pharmacodynamics trials.
- ☐ An immunologic concern for which accurate assessment requires in vitro development or validation of specific assays.

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<sup>6</sup> FDA Adverse Event Reporting System (FAERS)

<sup>7</sup> Active Risk Identification and Analysis (ARIA)

*Complete Q4.c when FAERS cannot provide the necessary data and Q4.b does not apply*

**c. FAERS data cannot be used to fully characterize the serious risk of interest because:**

*[Select all that apply then go to Q.4.d ]*

- ☐ Assessment of the serious risk necessitates calculation of the rate of occurrence (e.g., incidence or odds ratio) of the adverse event(s), and FAERS data cannot be used for such a calculation.
- ☐ The serious risk of concern has a delayed time to onset, or delayed time to detection after exposure (e.g., cancer), and FAERS data are more useful for detecting events that are closely linked in time to initiation of drug therapy.
- ☐ The serious risk of concern occurs commonly in the population (e.g., myocardial infarction) and FAERS data are more useful in detecting rare serious adverse events for which the background rates are low.
- ☐ Other

[If you selected "other," expand on the reason(s) why FAERS is not sufficient.]

*Complete Q4.d when the ARIA system cannot provide the necessary data and Q4.b does not apply.*

**d. The currently available data within the ARIA system cannot be used to fully characterize the serious risk of interest because:** *[Select all that apply then go to Q.4.e ]*

- ☐ Cannot identify exposure to the drug(s) of interest in the database.
- ☐ Serious risk (adverse event) of concern cannot be identified in the database.
- ☐ The population(s) of interest cannot be identified in the database.
- ☐ Long-term follow-up information required to assess the serious risk are not available in the database.
- ☐ Important confounders or covariates are not available or well represented in the database.
- ☐ The database does not contain an adequate number of exposed patients to provide sufficient statistical power to analyze the association between the drug and the serious risk of concern.
- ☐ The purpose of the evaluation is to rule out a modest relative risk, and observational studies, such as an ARIA analysis, are not well suited for such use.
- ☐ Other

[If you selected "other," expand on the reason(s) why ARIA is not sufficient.]

- e. If FAERS and the ARIA system are not sufficient for the purpose in Q1. and Q4.a, is a study sufficient?  
*[Select either “Yes” or “No” and provide the appropriate responses.]*

☐ Yes, a study is sufficient *[Explain your answer in the textbox and then go to Q.5]*

*[Explain why a study is sufficient]*

☐ No, a study is not sufficient *[Select all explanations that apply then go to Q.4.f]*

- ☐ Need to minimize bias and/or confounding via randomization
- ☐ Need for placebo control
- ☐ Need to capture detailed information about covariates or confounders that are either not routinely collected during the usual course of medical practice, or are not collected at the frequency needed for assessment of the safety issue (e.g. hourly blood glucose measures, etc.).
- ☐ Need pre-specified and prospective active data collection of the outcome/endpoint of interest
- ☐ Other

*[If you selected “other,” expand on the reason(s) why a study is not sufficient.]*

- f. ☐ Because a study is not sufficient, a clinical trial is required. *[Go to Q.5]*

5. **For all PMRs and PMCs:** What type of study or clinical trial is needed to achieve the goal described in Q1 or Q4.a above?

*[Select ONE OPTION only under either “Type of Study” or “Type of clinical Trial”]*

#### TYPE OF STUDY

- ☐ Drug interaction or bioavailability studies (nonclinical only)
- ☐ Epidemiologic (observational) study related to safe drug use
- ☐ Epidemiologic (observational) study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
- ☐ Immunogenicity study (nonclinical)
- ☐ Meta-analysis or pooled analysis of previous observational studies
- ☐ Nonclinical (animal) study (e.g., genotoxicity, carcinogenicity, reproductive toxicology)
- ☐ Nonclinical (in vitro) study (laboratory/microbiology resistance, receptor affinity)
- ☐ Pharmacogenetic or pharmacogenomic study
- ☐ Pharmacokinetic (PK) and/or pharmacodynamics (PD) study (nonclinical only)
- ☐ Quality CMC study (e.g., manufacturing, studies on impurities)
- ☐ Quality stability study
- ☐ Registry-based observational study

#### TYPE OF STUDY

☐ Other (describe) \_\_\_\_\_

#### TYPE OF CLINICAL TRIAL

- ☒ Combined PK/PD, safety and/or efficacy trial (*PREA\* PMRs only*)
- ☐ Dose-response clinical trial
- ☐ Dosing trial (e.g., alternative dosing schedule)
- ☐ Drug interaction or bioavailability clinical trial (clinical only)
- ☐ Immunogenicity trial (clinical)
- ☐ Meta-analysis or pooled analysis of previous clinical trials
- ☐ Pharmacogenetic or pharmacogenomic clinical trial
- ☐ Pharmacokinetic (PK) and/or pharmacodynamic (PD) clinical trial
- ☐ Primary efficacy clinical trial (i.e., with a primary efficacy endpoint; to further define efficacy; may include secondary safety endpoints)
- ☐ Primary safety clinical trial (e.g., to evaluate the long-term safety of a drug; to evaluate drug toxicity in a subpopulation; may include secondary efficacy endpoints) – *excludes SOT*
- ☐ Safety outcomes trial (SOT)\*\*
- ☐ Thorough Q-T clinical trial
- ☐ Other (describe) \_\_\_\_\_

\* Note that under PREA, clinical trials involving pediatric patients are specifically referred to as “studies.” However, for the purposes of this template, PREA investigations are categorized according to the established definitions of “studies” and “trials” (see Footnotes 3 and 4).

\*\* A safety outcomes trial (SOT) is defined as a large, prospective, randomized, controlled trial that is specifically designed and adequately powered to test a safety hypothesis using a clinical outcome, generally irreversible morbidity or mortality, as the primary trial endpoint. A cardiovascular outcomes trial (CVOT) is an example of an SOT.

#### SECTION D: PMR/PMC Additional Information

1. **This PMR/PMC applies to other drugs or applications (e.g. drugs in a therapeutic class; different formulations of the same drug).**

☐ Yes

☒ No

**2. This study or clinical trial focuses on the following special population(s) or circumstance(s):**

*[Select all that apply]*

- ☐ For non-PREA pediatric studies/trials only: Pediatric population
- ☐ Geriatric population
- ☐ Lactating/nursing mothers
- ☐ Medical Countermeasures (e.g. anthrax exposure, bioterrorism)
- ☐ Orphan or rare disease population
- ☐ Pregnant women
- ☐ Racial/ethnic population
- ☐ Not applicable

**3. (Complete if applicable) Additional comments about the PMR/PMC** (e.g., points or concerns not previously described; explanation for inclusion of milestones other than the 3 “core” milestones or draft protocol submission)

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**SECTION E: PMR/PMC Development Coordinator Statements<sup>8</sup>Error! Reference source not found.**

**1. The PMR/PMC is clear, feasible, and appropriate<sup>9</sup> because:** *[Select all that apply]*

- ☒ The study/clinical trial meets criteria for a PMR or a PMC.
- ☒ The objectives of the study/clinical trial are clear from the description of the PMR/PMC.
- ☒ The applicant has adequately justified the choice of milestone dates.
- ☒ The applicant has had sufficient time to review the PMR/PMC, ask questions, determine feasibility, and contribute to the development process.

**2. ☒ (If the PMR/PMC is a randomized controlled clinical trial) The following ethical considerations were made with regard to:**

- There is a significant question about the public health risks of the drug.
- There is not enough existing information to assess the public health risks of the drug.
- Information about the public health risks cannot be gained through a different kind of investigation.
- The trial will be appropriately designed to answer question about a drug’s efficacy or safety.

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<sup>8</sup> This section is completed by the PMR/PMC Development Coordinator, who is usually the OND division’s Deputy Director for Safety (DDS). See DEFINITIONS section of CDER MAPP 6010.9, *Procedures and Responsibilities for Developing Postmarketing Requirements and Commitments*.

<sup>9</sup> See POLICY section of CDER MAPP 6010.9.



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

3. ☒ **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.**

Insert electronic signature (usually the Deputy Director for Safety)

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/s/  
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DAWN WILLIAMS  
03/20/2018

TATIANA OUSSOVA  
03/20/2018



**Department of Health and Human Services  
Food and Drug Administration  
Center for Drug Evaluation and Research | Office of Surveillance and Epidemiology (OSE)**

**Epidemiology: ARIA Sufficiency Memo  
Version: 2018-01-24**

Date: March 16, 2018

Reviewer/  
Team Leader: Patricia Bright, PhD, MSPH  
Division of Epidemiology I

Deputy Division  
Director: Sukhminder K. Sandhu, PhD, MPH, MS  
Division of Epidemiology I

Subject: Active Risk Identification and Assessment (ARIA) Sufficiency Memo

Drug Name: Tildrakizumab

Application Type/#: BLA 761067

Applicant/Sponsor: Merck Sharp & Dohme Corp.

OSE RCM #: 2017-1627



## EXECUTIVE SUMMARY

Memo type	
-Initial	
-Interim	
-Final	X
Source of safety concern	
-Peri-approval	X
-Post-approval	
Is ARIA sufficient to help characterize the safety concern?	<u>Short-term</u> Lymphoma <u>Long-term</u> All malignancies
-Yes	X
-No	X
If "No", please identify the area(s) of concern.	For long-term malignancy:
-Surveillance or Study Population	
-Exposure	
-Outcome of Interest	X
-Covariates of Interest	X
-Surveillance Design/Analytic Tools	

## 1. BACKGROUND INFORMATION

### 1.1. Medical Product

Psoriasis is a chronic inflammatory skin disease which may undergo intermittent improvements and relapses in susceptible individuals over the course of their lifetime. Although traditional systemic therapies for psoriasis are effective, there may be a loss of efficacy during long-term use or patients may experience adverse events related to specific treatments.

Tildrakizumab, a subcutaneous (SC) biologic agent, is proposed for the treatment of moderate-to-severe plaque psoriasis. Tildrakizumab is a high affinity (297 pM) humanized immunoglobulin G1/kappa (IgG1/κ) monoclonal antibody that binds to IL-23/P19 subunit and blocks the interaction of human IL-23 with the IL-23 receptor [1]. IL-23, a naturally occurring cytokine, is involved in inflammatory and immune responses. Tildrakizumab inhibits the release of proinflammatory cytokines and chemokines.

Potential risks associated with immunomodulators used for psoriasis treatment include infection, malignancy, hypersensitivity reactions, injection site reactions and MACE [1]. The Office of New Drugs/Division of Dermatology and Dental Products (OND/DDDP) remains concerned about the potential for increased malignancy risk, which was not fully characterized during the clinical development program due to the general low frequency of these outcomes and long latency required for malignancy events.

On January 17, 2018, staff from the Office of Surveillance and Epidemiology (OSE) and OND/DDDP met to determine ARIA sufficiency for the assessment of malignancies and lymphoma following tildrakizumab exposure.

### 1.2. Describe the Safety Concern

As an immunomodulator, tildrakizumab poses a theoretical increased risk for malignancies based on its immunosuppressive mechanism of action. An increased malignancy risk mediated through immunosuppression is hypothesized to be a potential risk for all psoriasis biologics (Table 1).

**Table 1. Psoriasis biologics currently marketed in the United States**

Drug	Class	Approved for plaque psoriasis?	Postmarketing requirement for malignancy?	Approval date for plaque psoriasis
Stelara (ustekinumab)	interleukin-12 and -23 antagonists	Yes	Yes	September 25, 2009
Cosentyx (secukinumab)	interleukin-17A antagonist	Yes	Yes	January 21, 2015
Taltz (ixekizumab)	interleukin-17A antagonist	Yes	Yes	March 22, 2016
Siliq (brodalumab)	interleukin-17 receptor A (IL-17RA) antagonist	Yes	Yes	February 15, 2017
Tremfya (guselkumab)	interleukin-23 blocker	Yes	Yes	July 13, 2017

The clinical review was not finalized at the time of the January 17, 2018, meeting. However, the FDA Unireview states that the rate was not substantially higher than expected as compared to an outside control group:

“A comparison of the number of malignancies (other than cervical cancers in situ or NMSC) from Phase 2/3 trials (P003, P010 and P011) in the tildrakizumab groups with data from the Surveillance, Epidemiology, and End Results (SEER) Program of the National Cancer Institute (2010-2014)\* adjusted for age, sex, and race) indicated that the rate of these events in subjects with moderate to severe psoriasis treated with tildrakizumab for up to 64 weeks was no higher than that expected for the general U.S. population. Refer to the table below.” [2]

**Table 2: Exposure Adjusted Rates for Malignancy from the Pooled Phase 2/Phase 3 Trials Compared with the SEER Data**

Dose	Tildrakizumab 100 mg	Tildrakizumab 200 mg	Tildrakizumab 100/ 200 mg	Tildrakizumab 5/25/100 /200 mg
Person-years	968.3	910.3	1878.6	2010.5
Observed number of cancer cases** /100 subject years	4 (0.41)	2 (0.22)	6 (0.32)	7 (0.35)
Expected number cancer cases** /100 subject years based on SEER (2010-2014)	4.6 (0.48)	4.4 (0.48)	9 (0.48)	9.6 (0.48)

Source: Adapted from applicant table BLA 761067 SD 37 dated 12/1/2017, page 3

\* The calculation of person years excludes 47 subjects for which a single race category could not be assigned (race was either missing or multi-racial). None of these 47 subjects developed malignancies [other than cervical cancers in situ or non-melanoma skin cancers (NMSC)].

\*\* Excludes non-melanoma skin cancer, all in situ cancers and recurrent cancers (1 case of recurrent breast cancer)

Animal studies have not been conducted to evaluate the carcinogenicity of tildrakizumab.

The clinical evaluation of tildrakizumab had some notable parallels to the clinical evaluation for Tremfya (guselkumab), including the following:

“DDDP Clinical does not consider these clinical data to be a safety signal. The type of risk is considered to be a theoretical risk, where biological plausibility exists, yet clinical data are limited and not sufficient to support this suspicion of risk. DDDP described the safety concern as a variable-onset, where certain cancers may occur short-term, but there may also be a long-latency effect after initial exposure. The level of clinical concern is moderate, taking into account that malignancy is a very serious adverse event, but the concern is largely theoretical. DDDP was also specifically interested in assessing the risk of lymphomas, which may have a shorter latency compared to other malignancies.” [3]

### 1.3. FDAAA Purpose (per Section 505(o)(3)(B))

#### Purpose

Assess a known serious risk	
Assess signals of serious risk	
Identify unexpected serious risk when available data indicate potential for serious risk	X



#### **1.4. Statement of Purpose**

The purpose of the January 17, 2018, meeting was to determine whether ARIA could be used to assess malignancy risk and lymphoma risk when clinical data do not confirm a safety signal, but theoretical concerns indicate the potential for a serious risk. Meeting participants considered whether ARIA was sufficient to assess lymphoma in addition to assessing the broader category of all malignancies.

The regulatory goal of ARIA is signal detection (i.e. postmarketing surveillance). The anticipated regulatory impact is to further characterize malignancy risk to inform labeling decisions. Because the events of interest are rare, typically have long-term latency periods (except for lymphoma), and because multiple products are available for treatment of the underlying disease (plaque psoriasis), the sufficiency determination primarily rests upon the need for a large sample size, the availability of long-term follow-up (except for lymphoma), the availability of relevant covariates, and on the ensuing market uptake of tildrakizumab.

This ARIA Sufficiency Memo documents the findings from the January 17, 2018, meeting determination -- whether ARIA is sufficient to assess malignancy and lymphoma risk in the postmarketing setting after tildrakizumab exposure.

#### **2. Effect Size of Interest or Estimated Sample Size Desired**

Given that the clinical data do not confirm a safety signal, but represent theoretical concerns that indicate the potential for a serious risk, the regulatory goal for evaluating malignancy and lymphoma risk with ARIA is signal detection (postmarketing surveillance). However, given the availability of comparators, the ARIA assessment could support an inferential analysis by determining the incidence rate between tildrakizumab exposure and malignancy outcomes as compared to the incidence rates following exposure to other psoriasis biologic medications (Table 1). ARIA could also evaluate a class-based effect by comparing the incidence rate of malignancies following exposure to any psoriasis biologic medications as compared to the incidence rate of malignancies following exposure to non-biologic systemic medications for the indication of psoriasis.

It remains unknown whether the market uptake of tildrakizumab will be sufficient to detect a meaningful difference between malignancy (or lymphoma) rates following tildrakizumab exposure versus rates following exposure to other biologic psoriasis agents. Assessing a class-based effect (comparing malignancy or lymphoma rates following exposure to any psoriasis biologic medication to rates following exposure to non-biologic systemic medications) would likely yield a higher number of users with events and might increase the capacity to detect a difference in effect size.

Given that the using ARIA to assess the rate of all malignancies is deemed insufficient in this memo, no sample size is projected for the evaluation of all malignancies.

The marketing uptake of tildrakizumab will likely influence the ARIA approach for the lymphoma assessment: tildrakizumab versus other biologic psoriasis agents, or evaluating a class-based effect of the biologic psoriasis agents to non-biologic systemic psoriasis agents. Therefore, sample size requirements and the corresponding effect estimates will be described in the ARIA Planning Concept Brief that correspond to different projections for market uptake of tildrakizumab.

### **3. SURVEILLANCE OR DESIRED STUDY POPULATION**

#### **2.1 Population**

Tildrakizumab is indicated for the treatment of adults with moderate-to-severe plaque psoriasis who are candidates for systemic therapy or phototherapy. All patients with dispensings for tildrakizumab in Sentinel could be considered as candidates for monitoring for malignancy or lymphoma using ARIA. If tildrakizumab is subsequently approved for the treatment of other immunologically mediated inflammatory disorders, the analysis would benefit from stratifying by indication for tildrakizumab use.

If comparators are used to help facilitate interpretation of the incidence rate, a comparator population could consist of other psoriasis biologic medications listed in Table 1. If there is an interest in evaluating a class-effect, another comparator population could be non-biologic systemic medications used for psoriasis treatment. Both sets of comparators (other psoriasis biologic medications and non-biologic systemic medications) could be identified through the Sentinel health care claims data. The patient population (both tildrakizumab users and comparators) would require screening for the ICD10 (psoriasis) code of L40 to help limit the comparison to the psoriasis indication.

#### **2.2 Is ARIA sufficient to assess the intended population?**

ARIA can be used to identify patients with tildrakizumab dispensings in the claims data. If the underlying indication of psoriasis is needed to further target this population, the patient population can be screened for the ICD10 (psoriasis) code of L40.

Of relevance from the Tremfya (guselkumab) ARIA sufficiency evaluation:

“A Swedish study found the ICD-10 diagnosis codes for psoriasis to be well-validated, demonstrating a positive predictive value (PPV) ranging from 81-100%, depending on whether one or two codes were used in primary or specialized care. [4] Published validation studies using ICD-10 codes for psoriasis are not yet available in the United States. However, a recent validation study using Kaiser Permanente data found a PPV of 90% and sensitivity of 88% using at least one ICD-9 diagnosis code for psoriasis. [5] Although we did not identify any studies validating the ICD-10 diagnosis codes for psoriasis in the United States, data at least from the Swedish study suggests that performance would be adequate for surveillance purposes.” [3]

ARIA is sufficient to identify the intended population for this analysis and is in general, not a limiting factor. However, with several treatment options available to patients (Table 1), market uptake of tildrakizumab will affect whether enough users are available to further characterize malignancy or lymphoma risk given the rarity of these outcomes. The extent of market uptake can only be evaluated post-approval.

### **3 EXPOSURES**

#### **3.1 Treatment Exposure**

Patients with pharmacy benefits who receive at least one dispensing of tildrakizumab can be identified in health care claims data.

#### **3.2 Comparator Exposure**

The regulatory goal of this ARIA assessment is signal detection (i.e. postmarketing surveillance).



If a comparator is pursued to help facilitate interpretation of the incidence rate, a comparator population could consist of the other psoriasis biologic medications listed in Table 1. If there is an interest in evaluating a class-effect, another comparator population could be non-biologic systemic medications. Both sets of comparators (other psoriasis biologic medications and non-biologic systemic medications) could be identified through the Sentinel health care claims data.

### **3.3 Is ARIA sufficient to identify the exposure of interest?**

ARIA can capture tildrakizumab dispensings as well as dispensings of comparator agents; the ability to capture exposures is not a limiting factor undermining ARIA sufficiency.

## **4 OUTCOMES**

### **4.1 Outcomes of Interest**

The outcomes of interest are: 1) lymphoma and 2) overall malignancy.

A Workgroup<sup>a</sup> supporting Mini-Sentinel method development was tasked with developing algorithms for identifying cohorts of vulnerable groups within electronic healthcare data to facilitate active surveillance of risks from medical product exposure in these vulnerable cohorts [6]. One of the cohorts evaluated was non-cancer patients receiving immunologic treatment thought to suppress the immune system.

The same Workgroup also attempted to evaluate cohorts with cancer, but recommended that FDA primarily focus on the subcohorts of immunocompromised persons in the absence of cancer registry data. The group also stated that:

“First, consideration should be given to the identification of persons with hematopoietic cancers such as leukemias, lymphomas, myelomas...”

As part of the Workgroup’s deliverable, the Workgroup specified an algorithm for lymphoma that involved: Two or more diagnoses of cancer (ICD-9 codes) within 2 months (algorithm 2); this algorithm performed with a PPV of 62.83% and a sensitivity of 79.81%. [6]

The Workgroup also cautioned that:

“Cancers are not typically studied as a homogenous group, given differences in the histological type and primary site of the lesion—each that often has its distinct risk factors, screening requirements, pathology, clinical manifestations, diagnostic testing, differential diagnoses, staging, treatment and prognosis, as examples. Therefore, studies examining algorithms for identifying persons with any-type cancer are scant.” [6]

Therefore, while lymphoma may have a PPV and sensitivity that could be addressed through ARIA assessment, grouping all malignancies together and trying to determine whether malignancies in general (encompassing heterogeneous outcomes that differ in respect to their ability to be identified in claims data) offers less scientific rigor.

### **4.2 Is ARIA sufficient to assess the outcomes of interest?**

While evaluating “all malignancies” as a broad category has limitations as discussed above, the

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<sup>a</sup> The Workgroup, to support method development for the Mini-Sentinel pilot, resulted from a collaboration between the Center for Pharmacoepidemiology Research and Training (CPeRT) at the Perelman School of Medicine of the University of Pennsylvania (as lead site), the University of Iowa, the University of Massachusetts/Meyers Primary Care Institute, the Kaiser Permanente Center for Health Research, the Group Health Research Institute, the Harvard Pilgrim Health Care Institute Mini-Sentinel Operations Center (MSOC), and FDA [6].



Tremfya (guselkumab) ARIA Sufficiency Memo provided the following additional information on validation:

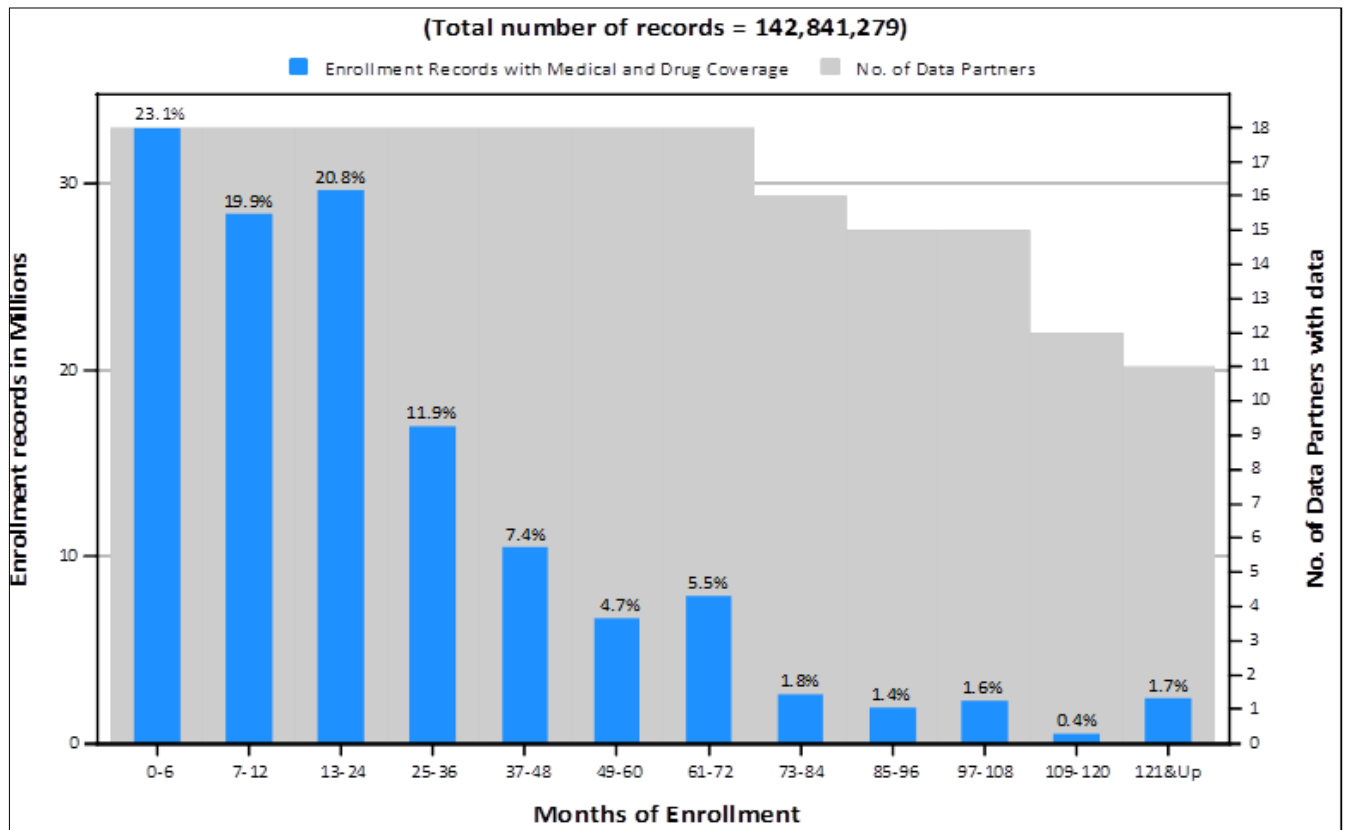
“Validation of malignancy outcomes has not been assessed in Sentinel. However, there have been published validation studies using health care claims data for malignancy. In Medicare, a 63% positive predictive value was achieved using a complex algorithm. [7 ] Different claims-based definitions used for specific types of incident cancers all had very high specificity (~99%); however, the sensitivity varied between 40 and 90% by type of cancer. Positive predictive value (PPV) also varied by type of cancer. Hence, depending on the type of cancer of interest, health care claims data may be acceptable. The various definitions used by Setoguchi et al. included 1) a combination of diagnosis and procedure codes on the same day or within the same hospitalization; 2) two diagnoses of specific cancer within two months; 3) either definition 1 or definition 2. For lymphoma, specificity was  $\geq 99.7\%$  for all 3 definitions, sensitivity ranged from 55.2% to 83.3%, and PPV ranged from 56.6% to 62.8%, for the 3 definitions. A study validating ICD-9 codes using Veteran Affairs data, found non-Hodgkin’s lymphoma to have the highest PPV (91%) with 100% sensitivity. [8] The PPV and sensitivity for Hodgkin’s lymphoma were not stated in the article. A Mini- Sentinel methods paper states that there are multiple types of lymphoma and multiple classifications for categorizing the types of lymphoma. [9 ] These can be based on etiology (T-cell and B-cell lymphomas) or separated based on expected outcomes (e.g., curability). Validation studies for the many specific types of lymphoma are not available for claims data, and therefore, it is unknown whether there are certain types of lymphoma which may have poor validation.” [3]

“In summary, the Medicare validation study of lymphoma in general performed reasonably well (i.e., PPV: 57-63%). The VA study showed high PPV (i.e., 91%) for non-Hodgkin’s lymphoma. We consider these PPV values to be acceptable for the purpose of surveillance.” [3]

None-the-less, the need for long term follow-up undermines ARIA sufficiency for malignancies with long latency periods. (Lymphoma does not fall into this category since it does not require a long latency period.) Figure 1<sup>b</sup> below depicts, enrollment records by months of enrollment. Of note, approximately 75% of enrollment records in Sentinel correspond to 3 years or less of available follow-up data. This lack of follow-up time, in combination with those malignancies that are of low frequency, and variable PPV, pose a particular threat to ARIA sufficiency for the broad category of all malignancy outcomes.

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<sup>b</sup> This data in Figure 1 reflects numbers prior to CMS joining Sentinel as a data partner.



**Figure 1. Number of Enrollment Records by Length of Enrollment in the Sentinel database [10]**

## 5 COVARIATES

### 5.1 Covariates of Interest

Covariates of interest typically include demographic variables, comorbidities, and concomitant medications. These can be obtained through claims data. However, other covariates involving behavioral risks (such as smoking, obesity, or alcohol use) or medical history (such as family history of the malignancy) are not readily obtained in claims data. Furthermore, duration and severity of psoriasis (or proxies for duration or severity) may or may not be evident from the claims data.

### 5.2 Is ARIA sufficient to assess the covariates of interest?

While some covariate data is available from claims data, some is not. The impact of the missing covariate data will depend on the characteristics of the specific malignancies, since this is a heterogeneous group of outcomes. For example, covariate data in smoking would be critical to the interpretation of lung cancer risk.

The Tremfya (guselkumab) ARIA Sufficiency Memo offers the following perspective on the impact of missing covariate data as it pertains to lymphoma risk:

“Specific to lymphomas, obesity and smoking are considered to be weak risk factors for lymphomas in general and would not be critical for our analyses. [11,12,13] However, some additional potential confounders include infections (e.g., Epstein-Barr virus, HIV, and Hepatitis C). HIV and Hepatitis C should be captured in diagnosis codes in Sentinel, as these are serious chronic diseases. Epstein-Barr virus or mononucleosis may be challenging as

these are less serious and may have occurred in the past, not captured in Sentinel. However, because Epstein-Barr virus is more common and less serious and may have occurred in the distant past, likely most data sources would have difficulty capturing this infection, as a patient may not even be aware that they had this virus.” [3]

## 6 SURVEILLANCE DESIGN / ANALYTIC TOOLS

### 6.1 Surveillance or Study Design

The study design involves identifying the incidence of lymphoma in patients exposed to tildrakizumab; the study would not address the incidence of all malignancies due to the challenges to ARIA sufficiency described in Section 4.2. Given the availability of comparators that would strengthen the interpretation of the ARIA assessment, the study design could support an inferential analysis by determining the incidence rate between tildrakizumab exposure and malignancy outcomes as compared to the incidence rates following exposure to other psoriasis biologic medications. ARIA could also evaluate a class-based effect by comparing the incidence rate of malignancies following exposure to any psoriasis biologic medications as compared to the incidence rate of malignancies following exposure to non-biologic systemic medications for the indication of psoriasis.

Given the projected PPV for lymphoma of approximately 63% (Section 4.1), potential misclassification of lymphoma will bias risk estimates toward the null. Table 3 can be used to determine whether the impact of misclassification might negate the ability for this inferential analysis to detect a difference between the exposure and comparator, undermining the inferential analysis.

**Table 3<sup>cd</sup>: Observed Relative Risk in the case of Non-Differential Misclassification**

		PPV in the Comparator Group													
		0.40	0.45	0.50	0.55	0.60	0.65	0.70	0.75	0.80	0.85	0.90	0.95	1.00	
True RR	1.0	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	
	1.5	1.20	1.22	1.25	1.27	1.30	1.32	1.35	1.37	1.40	1.42	1.45	1.47	1.50	
	2.0	1.40	1.45	1.50	1.55	1.60	1.65	1.70	1.75	1.80	1.85	1.90	1.95	2.00	
	2.5	1.60	1.67	1.75	1.82	1.90	1.97	2.05	2.12	2.20	2.27	2.35	2.42	2.50	
	3.0	1.80	1.90	2.00	2.10	2.20	2.30	2.40	2.50	2.60	2.70	2.80	2.90	3.00	
	3.5	2.00	2.12	2.25	2.37	2.50	2.62	2.75	2.87	3.00	3.12	3.25	3.37	3.50	
	4.0	2.20	2.35	2.50	2.65	2.80	2.95	3.10	3.25	3.40	3.55	3.70	3.85	4.00	
	4.5	2.40	2.57	2.75	2.92	3.10	3.27	3.45	3.62	3.80	3.97	4.15	4.32	4.50	
	5.0	2.60	2.80	3.00	3.20	3.40	3.60	3.80	4.00	4.20	4.40	4.60	4.80	5.00	
	5.5	2.80	3.02	3.25	3.47	3.70	3.92	4.15	4.37	4.60	4.82	5.05	5.27	5.50	
	6.0	3.00	3.25	3.50	3.75	4.00	4.25	4.50	4.75	5.00	5.25	5.50	5.75	6.00	
	6.5	3.20	3.47	3.75	4.02	4.30	4.57	4.85	5.12	5.40	5.67	5.95	6.22	6.50	
	7.0	3.40	3.70	4.00	4.30	4.60	4.90	5.20	5.50	5.80	6.10	6.40	6.70	7.00	
	7.5	3.60	3.92	4.25	4.57	4.90	5.22	5.55	5.87	6.20	6.52	6.85	7.17	7.50	
	8.0	3.80	4.15	4.50	4.85	5.20	5.55	5.90	6.25	6.60	6.95	7.30	7.65	8.00	
	8.5	4.00	4.37	4.75	5.12	5.50	5.87	6.25	6.62	7.00	7.37	7.75	8.12	8.50	
9.0	4.20	4.60	5.00	5.40	5.80	6.20	6.60	7.00	7.40	7.80	8.20	8.60	9.00		
9.5	4.39	4.82	5.25	5.67	6.10	6.52	6.95	7.37	7.80	8.22	8.65	9.07	9.50		
10.0	4.59	5.05	5.50	5.95	6.40	6.85	7.30	7.75	8.20	8.65	9.10	9.55	10.00		
Underlying Outcome Rate: 1/1000 person-years (produces worst case scenario estimate of bias)															

According to the projections in Table 3, a PPV of 60% would dampen a true relative risk (RR) of 2.0 to an observed RR of 1.60. A slightly higher PPV of 65% would dampen a true RR of 2.0 to an observed RR of 1.65. If the true association is more modest, such as a RR of 1.5, a PPV of 60% and 65% would diminish the observed RR to 1.30 and 1.32, respectively. Therefore,

<sup>c</sup> Table 3 provided by Dr. Judy Maro, Harvard Pilgrim Health Care Institute.

<sup>d</sup> Table 3 can inform power calculations so that power estimates correspond to the likely “observed risk,” rather than the “true” or expected risk.



while a lower PPV reduces the ability to detect a difference between the exposure and comparator, the impact of a PPV of 63% would not be of a magnitude likely to undermine the inferential analysis.

The analytical tools to conduct a surveillance study, and even an inferential assessment in this context, are available through ARIA.

## **6.2 Is ARIA sufficient with respect to the design/analytic tools available to assess the question of interest?**

The analytic tools in ARIA are not a major limiting factor to feasibility. ARIA offers the tools needed to both describe the incidence of lymphoma and to conduct an inferential assessment comparing incidence rates to other psoriasis biologic medications and non-biologic systemic medications.

## **7 NEXT STEPS**

The January 17, 2018, meeting determined that ARIA was **sufficient for assessing the incidence of lymphoma and sufficient to support an inferential analysis comparing the lymphoma rate among tildrakizumab exposed patients to lymphoma rates among patients exposed to comparators**, but **insufficient for assessing all malignancies as a general category**. For the outcome of “all malignancies,” the ARIA assessment would be compromised through short length of follow-up in Sentinel, variable validation characteristics and sensitivity by malignancy, and missing data on covariates that might be important to the interpretation of risk across all malignancies.

The next step for assessing the lymphoma risk following tildrakizumab exposure is to fill out the ARIA Planning Concept Brief that prompts Sentinel’s routine monitoring of market uptake for tildrakizumab. If market uptake reaches a level sufficient to trigger the analysis, FDA investigators can fill in the Analytic Concept Brief and launch the assessment.

Because ARIA was deemed insufficient to assess “all malignancies,” as a broad category, DDDP may choose to issue a postmarketing requirement to the Sponsor to evaluate malignancy risk following tildrakizumab exposure. This would be consistent with postmarketing requirements for the other products in the class.

FDA preliminary thoughts on potential PMRs appears to use the Tremfya (guselkumab) PMR language as a model for a tildrakizumab PMR is as follows:

“Conduct a prospective, observational study to assess the long-term safety of tildrakizumab compared to other therapies used in the treatment of adults with moderate to-severe plaque psoriasis who are candidates for systemic therapy or phototherapy in the course of actual clinical care. The study’s primary outcome is long-term malignancy. Secondary outcomes include, but are not limited to, serious infections, tuberculosis, opportunistic infections, hypersensitivity reactions, autoimmune disease, neurologic or demyelinating disease, cardiovascular, gastrointestinal and hematologic adverse events. Describe and justify the choice of appropriate comparator population(s) and estimated background rate(s) relative to tildrakizumab-exposed patients; clearly define the primary comparator population for the primary objective. Design the study around a testable hypothesis to assess, with sufficient sample size and power, a clinically meaningful increase in malignancy risk above the comparator background rate(s), with a prespecified statistical analysis method. Specify concise case definitions and validation algorithms for both primary and secondary outcomes. For the tildrakizumab-exposed and comparator(s) cohorts, clearly define the study drug initiation period and any exclusion



and inclusion criteria. Enroll patients over an initial 4 year period and follow for a minimum of 8 years from the time of enrollment.” [14]

The finalized PMR language will be issued upon approval.

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- <sup>8</sup> Park LS, Tate JP, Rodriguez-Barradas MC, et al. Cancer incidence in HIV-infected versus uninfected veterans: Comparison of cancer registry and ICD-9 code diagnoses. *J AIDS Clin Res*. 2014; 5:7.
- <sup>9</sup> Schumock GT, Lee TA, Pickard AS, et al. Mini-Sentinel Methods: Alternative methods for health outcomes of interest validation. August 31, 2013.  
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- <sup>10</sup> Source: Michael D. Nguyen, MD. FDA Sentinel Program Lead.
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- <sup>14</sup> <https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm?event=overview.process&ApplNo=761061>, accessed February 17, 2018.



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03/19/2018

MICHAEL D NGUYEN  
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ROBERT BALL  
03/19/2018

## Clinical Inspection Summary

<b>Date</b>	February 7, 2018
<b>From</b>	Bei Yu, Ph.D., Reviewer Good Clinical Practice Assessment Branch Division of Clinical Compliance Evaluation Office of Scientific Investigations (OSI)
<b>To</b>	Dawn Williams, Regulatory Project Manager Melinda McCord, Clinical Reviewer Kevin Clark, Clinical Reviewer Gordana Diglisic, Clinical Team Leader Division of Dermatology and Dental Products (DDDP)
<b>BLA #</b>	761067
<b>Applicant</b>	Merck Sharp & Dohme Corp.
<b>Drug</b>	Tildrakizumab
<b>NME</b>	Yes
<b>Review Priority</b>	Standard Review
<b>Proposed Indication</b>	Moderate to Severe Plaque Psoriasis
<b>Consultation Request Date</b>	May 2, 2017
<b>Summary Goal Date</b>	February 9, 2018
<b>Action Goal Date</b>	March 9, 2018
<b>PDUFA Date</b>	March 23, 2018

### I. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

The clinical sites of Drs. Lee, Gupta, Gooderham, Szepietowski, and Claman were inspected in support of BLA 761067. The sponsor, Merck Sharp & Dohme Corp., was also inspected. Based on the results of these inspections, the studies appear to have been conducted adequately, and the data generated by these sites and submitted by the sponsor appear acceptable in support of the respective indication.

The final classification of the inspections of five clinical investigators (Drs. Lee, Gupta, Gooderham, Szepietowski, and Claman) was No Action Indicated (NAI). The preliminary classification of the inspection of the sponsor is Voluntary Action Indicated (VAI).

### II. BACKGROUND

The Applicant submitted this BLA to support the use of tildrakizumab for the treatment of adults with moderate-to-severe plaque psoriasis. Inspections were requested for the following protocols in support of this application:

**Protocol MK-3222 P010**, entitled “A 64-Week, Phase 3, Randomized, Placebo-Controlled, Parallel Design Study to Evaluate the Efficacy and Safety/Tolerability of Subcutaneous



Tildrakizumab (SCH 900222/MK-3222), Followed by an Optional Long-Term Safety Extension Study, in Subjects With Moderate-to-Severe Chronic Plaque Psoriasis”.

This study was conducted at 118 clinical sites in Australia, Japan, UK, and North America between December 2012 and October 2015 (base study). A total of 772 subjects were enrolled.

This was a Phase 3, multicenter, randomized, double-blind, placebo controlled, parallel-group study. The duration of the base study was up to 88 weeks for each subject. This included a 4-week screening period, a 12-week Part 1 period, a 16-week Part 2 period, a 36-week Part 3 period, and a 20-week follow-up period. Enrolled subjects were randomized on Day 1 (Week 0, Visit 2) in a 2:2:1 ratio to one of the 3 treatment arms: tildrakizumab 200 mg, tildrakizumab 100 mg, or placebo. Following the end of Part 1, at Week 12, all subjects were assessed for PASI (Psoriasis Area and Severity Index) and PGA (Physician’s Global Assessment) response.

The co-primary efficacy endpoints were:

- proportion of subjects with PASI 75 response (at least 75% improvement in the PASI) at Week 12
- proportion of subjects with a PGA score of “clear” or “minimal”, with at least a 2-grade reduction from Baseline, at Week 12.

**Protocol MK-3222 P011**, entitled “A 52-Week, Phase 3, Randomized, Active Comparator and Placebo-Controlled, Parallel Design Study to Evaluate the Efficacy and Safety/ Tolerability of Subcutaneous Tildrakizumab (SCH 900222/MK-3222), followed by an Optional Long-Term Safety Extension Study, in Subjects With Moderate-to-Severe Chronic Plaque Psoriasis”

This study was conducted at 132 clinical sites in Europe, Israel, and North America between February 2013 and September 2015 (base study). A total of 1090 subjects were enrolled.

This was a Phase 3, multicenter, randomized, double-blind, active comparator, placebo-controlled, parallel-group study. The duration of the base study was up to 76 weeks for each subject. This included a 4-week screening period, a 12-week Part 1 period, a 16-week Part 2 period, a 24-week Part 3 period, and a 20-week follow-up period. Enrolled subjects were randomized on Day 1 (Week 0, Visit 2) in a 2:2:1:2 ratio to one of the 4 treatment arms: tildrakizumab 200 mg, tildrakizumab 100 mg, placebo, and etanercept. Following the end of Part 1, at Week 12, all subjects were assessed for PASI and PGA response.

The co-primary efficacy endpoints were the same as for Study P010.

### **Rationale for Site Selection**

Drs. Lee’s, Gooderham’s, Gupta’s, and Claman’s sites were selected for inspection mainly due to a high site efficacy effect and the fact that these investigators had no prior history of GCP inspections. Dr. Szepietowski’s site was selected for inspection mainly due to a high enrollment and a high site efficacy effect.

**III. RESULTS (by site):**

<b>Site #/ Name of CI/ Address</b>	<b>Protocol # / # of Subjects Enrolled</b>	<b>Inspection Dates</b>	<b>Classification</b>
Site #127 <b>Lee, Patricia</b> 1401 Binz Street Suite 200 Houston, TX 77004	MK3222-P010 Subjects: 20	11 – 15, 18 Sep 2017	NAI
Site #1107 <b>Gupta, Aditya</b> 645 Windermere Road London, Ontario N5X 2P1 Canada	MK3222-P010 Subjects: 14	31 Jul – 4 Aug 2017	NAI
Site #1111 <b>Gooderham, Melinda</b> 775 Monaghan Road Peterborough, Ontario K9J 5K2 Canada	MK3222-P010 Subjects: 17	14 – 16 Aug 2017	NAI
Site #4807 <b>Szepietowski, Jacek</b> ul. Tytusa ChaBubiDskiego 1 Wroclaw, Dolnoslaskie 50-368 Poland	MK3222-P011 Subjects: 34	07 – 11 Aug 2017	NAI
Site #172 <b>Claman, Cassandra</b> 1025 S. 6th Street Springfield, IL 62703	MK3222-P011 Subjects: 23	09 – 16 Aug 2017	NAI
Sponsor <b>Merck &amp; Co.</b> 126 E. Lincoln Avenue, Rahway, NJ 07065	MK3222-P010 MK3222-P011	16 - 30 Oct 2017	VAI*

Key to Compliance Classifications

NAI = No deviation from regulations.

VAI = Deviation(s) from regulations.

\*Pending = Preliminary classification based on information in Form FDA 483 or preliminary communication with the field; EIR has not been received from the field, or complete review of EIR is pending. Final classification occurs when the post-inspectional letter has been sent to the inspected entity.

Of note, clinical investigators were supposed to complete the PASI and PGA scores on a tablet provided by the vendor (b) (4). For the inspections of Drs. Claman, Gooderham, and Szepietowski, the PASI and PGA source data were not available at the sites. We requested certified CDs (with audit trails) for these three sites from ERT with the PASI and PGA scores. These were compared with the data line listings. No discrepancies were found.

At Dr. Gupta's site, the PASI and PGA scales had been completed on paper. For the last inspection, that of Dr. Lee, a CD from ERT with the PASI and PGA source data was available at the site.

### **Clinical Investigator Sites**

#### **1. Patricia Lee, M.D.**

At this site for Protocol MK3222-P010, a total of 25 subjects were screened and 20 subjects were enrolled, 16 of whom completed the base study. The informed consent forms for all 25 screened subjects were reviewed to ensure that subjects were properly consented.

The records for all 20 enrolled subjects were reviewed. These included, but were not limited to, medical records, individual subject files, subject diaries, IRB correspondences, and drug accountability logs.

The primary efficacy endpoint data were verifiable. There was no evidence of underreporting of adverse events.

A Form FDA 483 was not issued at the conclusion of the inspection. However, discussion items included the fact that Subject (b) (6) was on a prohibited medication (Topicort, 0.05%, BID) for about 5 days due to a rash on her right inner arm. It appears that the use of Topicort happened around Week 40, which is past the time of the primary efficacy endpoint.

Of note, in addition to the protocol-specified PASI and PGA, Dr. Lee conducted an efficacy assessment called the Investigator's Global Assessment of Dermatology for the Whole Body (IGA). According to the sponsor, use of paper IGA, in addition to PASI and PGA, was unique to this site as this has been standard practice at this center since 2010. This site stopped the use of paper assessments for P010 in November of 2013, as per standard study procedures, after a communication from the CRO was sent to all sites reiterating the tablet should be the source for physician assessments and re-training was provided by the CRA on using the tablet for PASI and PGA. The site only utilized the tablet for those assessments thereafter.

According to the sponsor, for all but 5 instances, site 0127 confirmed the IGA was registered on paper and PGA was registered directly into the tablet as source. In five instances where the site had technical issues accessing the PGA in the tablet, the PASI and IGA only were recorded on paper and entered into the EDC through a Data Clarification Form. In all 5 cases, the subjects were clear with no evidence of erythema, plaque elevation or scaling and therefore their scores were 0, which would be the identical score for either the IGA or PGA.

**2. Aditya Gupta, M.D.**

At this site for Protocol MK3222-P010, 22 subjects were screened and 14 subjects were enrolled, all of whom completed the base study. The informed consent forms for all 22 screened subjects were reviewed to ensure that subjects were properly consented.

The records reviewed included, but were not limited to, informed consent forms, paper PASI and PGA, medical records, adverse events, laboratory results, drug accountability records, clinical investigator agreements, financial interest documents, and training records.

The primary efficacy endpoint data were verifiable. Except for a case of hyperglycemia in a subject with a history of diabetes, there was no evidence of underreporting of adverse events.

A Form FDA 483 was not issued at the conclusion of the inspection.

**3. Melinda Gooderham, M.D.**

At this site for Protocol MK3222-P010, 18 subjects were screened and 17 subjects were enrolled, 14 of whom completed the base study. The informed consent forms for all subjects were reviewed to ensure that subjects were properly consented.

The records reviewed included, but were not limited to, training records, sponsor correspondence, Ethics Committee correspondence, drug accountability, monitoring records, and individual subject files.

A Form FDA 483 was not issued at the conclusion of the inspection.

**4. Jacek Szepietowski, M.D.**

At this site for Protocol MK3222-P011, 39 subjects were screened and 34 subjects were enrolled. The informed consent forms for all subjects were reviewed to ensure that subjects were properly consented.

The records for 22 subjects were reviewed in full. These included, but were not limited to, training records, sponsor correspondence, Ethics Committee (EC) correspondence, drug accountability, monitoring records, and individual subject files.

A Form FDA 483 was not issued at the conclusion of the inspection. However, discussion items included the fact that the clinical investigator did not record the reason why abnormal ALT and/or AST lab tests for three subjects (b) (6) during a period of time in the study were not considered to be clinically significant. The ALT was as high as 124 U/L for one subject. The clinical investigator stated that he believed the elevated ALT/AST values were due to the subjects' alcohol intake.

**5. Cassandra Claman, M.D.**

At this site for Protocol MK3222-P011, 31 subjects were screened and 23 subjects were enrolled, all of whom completed the base study. The informed consent forms for all 23 enrolled subjects were reviewed to ensure that subjects were properly consented.

Records reviewed included, but were not limited to, IRB approvals, subject electronic medical records, paper worksheets for information specific to the protocols, monitoring reports, site signature and responsibility logs, site training logs, drug accountability records, and all versions of the Form FDA 1572. There was no evidence of underreporting of adverse events.

A Form FDA 483 was not issued at the conclusion of the inspection. However, discussion items included the following errors in adverse event (AE) reporting:

- For Subject (b) (6) the end date (b) (6) for both AEs of rhinovirus infection and acute sinusitis was not entered into the eCRF form;
- For Subject (b) (6) the site mistakenly reported three AE's attributed to Subject 012. The AE's of intertrigo, medium brown mole, and inframammary strep infection were reported correctly for (b) (6) but were also entered by mistake to the eCRF for Subject (b) (6)
- For Subject (b) (6) the paper source documentation lists the AE's of allergic rhinitis and eustachian tube dysfunction as moderate severity. The eCRF and the sponsor data table lists the severity as mild. In addition, the site source documentation lists an end date for the AE of "localized inflammation 2<sup>nd</sup> day to injection" as (b) (4), (b) (6). No end date appears in the eCRF or the sponsor data table.

**Sponsor Site****Merck Sharp & Dohme Corp.**

This was a joint FDA-EMA inspection. The inspection covered Protocols P010 and P011, focusing on the five clinical investigators that FDA had inspected. In addition, due to some monitoring issues discovered during EMA's inspection of Dr. Georg Popp (Site #4901; n=11) and Dr. Kristian Reich (Site #4924; n=26), both in Germany, for Study P011, monitoring records for these sites were reviewed.

An FDA Form 483, Inspectional Observations, was issued at the conclusion of the inspection for the Study P011. Observations included:



(b) (4)



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Bei Yu, Ph.D.  
Pharmacologist  
Good Clinical Practice Assessment Branch  
Division of Clinical Compliance Evaluation  
Office of Scientific Investigations

CONCURRENCE:

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Phillip Kronstein, M.D  
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Kassa Ayalew, M.D., M.P.H  
Branch Chief  
Good Clinical Practice Assessment Branch  
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CC:

Central Doc. Rm. / BLA 761067  
DDDP /Medical Team Leader/Gordana Diglisic  
DDDP /Project Manager/Dawn Williams  
DDDP/MO/Melinda McCord and Kevin Clark  
OSI/DCCE/ Division Director/ Ni Khin  
OSI/DCCE/Branch Chief/ Kassa Ayalew  
OSI/DCCE/Team Leader/Phillip Kronstein  
OSI/DCCE/GCP Reviewer/Bei Yu  
OSI/ GCP Program Analysts/ Joseph Peacock/Yolanda Patague

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02/07/2018

KASSA AYALEW  
02/08/2018



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

**PATIENT LABELING REVIEW**

Date: December 22, 2017

To: Kendall Marcus, MD  
Director  
**Division of Dermatology and Dental Products (DDDP)**

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

Barbara Fuller, RN, MSN, CWOCN  
Team Leader, Patient Labeling  
**Division of Medical Policy Programs (DMPP)**

From: Morgan Walker, PharmD, MBA, CPH  
Patient Labeling Reviewer  
**Division of Medical Policy Programs (DMPP)**

Kyle Snyder, PharmD  
Regulatory Review Officer  
**Office of Prescription Drug Promotion (OPDP)**

Subject: Review of Patient Labeling: (Medication Guide (MG))

Drug Name (established name): TRADEMARK (tildrakizumab)

Dosage Form and Route: injection, for subcutaneous use

Application Type/Number: BLA 761067

Applicant: Merck Sharp & Dohme Corp.

## 1 INTRODUCTION

On March 24, 2017, Merck Sharp & Dohme Corp. submitted for the Agency's review a Biologics License Application (BLA) 761067 for TRADEMARK(tildrakizumab) injection. The proposed indication for TRADEMARK (tildrakizumab) is for the treatment of adults with moderate-to-severe plaque psoriasis who are candidates for system therapy or phototherapy.

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 Dermatology and Dental Products (DDDP) on October 20, 2017 and October 4, 2017, for DMPP and OPDP, respectively, to review the Applicant's proposed Medication Guide (MG) for TRADEMARK (tildrakizumab) injection.

## 2 MATERIAL REVIEWED

- Draft TRADEMARK (tildrakizumab) injection MG received on March 24, 2017, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on December 12, 2017.
- Draft TRADEMARK (tildrakizumab) injection Prescribing Information (PI) received on March 24, 2017, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on December 12, 2017.
- Approved TREMFYA (guselkumab) comparator labeling dated July 13, 2017.

## 3 REVIEW METHODS

To enhance patient comprehension, materials should be written at a 6<sup>th</sup> to 8<sup>th</sup> grade reading level, and have a reading ease score of at least 60%. A reading ease score of 60% corresponds to an 8<sup>th</sup> grade reading level. In our review of the MG the target reading level is at or below an 8<sup>th</sup> grade 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 reformatted the MG document using the Arial font, size 10.

In our collaborative review of the MG we:

- simplified wording and clarified concepts where possible
- ensured that the MG is consistent with the Prescribing Information (PI)
- removed unnecessary or redundant information
- ensured that the MG is 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 meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)
- ensured that the MG is consistent with the approved comparator labeling where applicable.

#### **4 CONCLUSIONS**

The MG is 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 is 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.

Please let us know if you have any questions.

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MORGAN A WALKER  
12/22/2017

KYLE SNYDER  
12/22/2017

BARBARA A FULLER  
12/22/2017

LASHAWN M GRIFFITHS  
12/22/2017

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

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

**Memorandum**

**Date:** December 21, 2017

**To:** Kevin Clark  
Clinical Reviewer  
Division of Dermatology and Dental Products (DDDP)

Gordana Diglisic, MD  
Cross Discipline Team Leader (DDDP)

Dawn Williams  
Regulatory Project Manager (DDDP)

**From:** Kyle Snyder, PharmD  
Regulatory Review Officer  
Office of Prescription Drug Promotion (OPDP)

**CC:** Matthew Falter, PharmD  
Team Leader (OPDP)

**Subject:** OPDP Labeling Comments for TRADEMARK™ (tildrakizumab) injection,  
for subcutaneous use

**BLA:** 761067

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In response to DDDP's consult request dated October 4, 2017, OPDP has reviewed the proposed prescribing information (PI) for BLA 761067, TRADEMARK™ (tildrakizumab) injection, for subcutaneous use.

**PI:** OPDP's comments on the proposed labeling are based on the draft PI received by electronic mail from DDDP on December 12, 2017. Comments on the proposed PI are provided below.

**MG:** A combined OPDP and Division of Medical Policy Programs (DMPP) review will be completed for the MG, and comments on the proposed MG will be sent under separate cover.

Thank you for your consult. If you have any questions, please contact Kyle Snyder at (240) 402-8792 or [kyle.snyder@fda.hhs.gov](mailto:kyle.snyder@fda.hhs.gov).

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/s/  
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KYLE SNYDER  
12/21/2017



DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

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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

**Pregnancy and Lactation Labeling Rule (PLLR) Labeling Review**

**Date:** December 21, 2017 **Date Consulted:** May 3, 2017

**From:** Christos Mastroyannis, M.D., Medical Officer, Maternal Health  
Division of Pediatric and Maternal Health (DPMH)

**Through:** Tamara Johnson, M.D., M.S., Team Leader, Maternal Health  
Division of Pediatric and Maternal Health  
  
Lynne P. Yao, M.D., Division Director,  
Division of Pediatric and Maternal Health

**To:** Division of Dermatology and Dental Products (DDDP)

**Drug:** Ilumya (tildrakizumab) injection, for subcutaneous use

**Drug Class:** Humanized monoclonal antibodies (IL23 antagonist)

**BLA:** 761067

**Subject:** Pregnancy and Lactation Labeling as part of original BLA

**Proposed Indication:** The treatment of adult patients with moderate-to-severe plaque psoriasis who are candidates for systemic therapy or phototherapy

**Applicant:** Merck Sharp & Dohme Corp

**Materials Reviewed:**

- Applicant's proposed labeling
- March 23, 2017, Applicant's submission
- May 3, 2017 DDDP's request to DPMH for labeling review

**Consult Question:** Assist with Pregnancy and Lactation Labeling

## INTRODUCTION

### REGULATORY HISTORY

The applicant, Merck Sharp & Dohme Corp, submitted an original 351(a) biologic license application (BLA761067) for Ilumya (tildrakizumab) injection on March 23, 2017. The proposed indication is for the treatment of adults with moderate to severe plaque psoriasis who are candidates for systemic therapy or phototherapy. The Division of Dermatology and Dental Products (DDDP) consulted the Division of Pediatric and Maternal Health (DPMH) on May 3, 2017, to assist with reviewing the Pregnancy and Lactation subsections of labeling to comply with the Pregnancy and Lactation Labeling Rule (PLLR) format.

This review provides recommended revisions and structuring of information related to the Pregnancy, Lactation, and Females and Males of Reproductive Potential subsections in labeling in order to provide clinically relevant information for prescribing decisions and to comply with current PLLR regulatory requirements.

### BACKGROUND

#### Drug Characteristics

- Ilumya (tildrakizumab) is a humanized IgG1/k monoclonal antibody that selectively binds to the p19 subunit of interleukin (IL)-23. IL-23 is a naturally occurring cytokine, composed of 2 subunits (IL-23p19 and IL-12/23p40), that is involved in inflammatory and immune responses.
- Tildrakizumab is produced in a recombinant Chinese hamster ovary (CHO) cell line
- Molecular weight of 147 kilodaltons
- Half-life of 23.4 days in subjects with plaque psoriasis.
- Absolute bioavailability of 73-80%
- Other drugs in the IL 23 antagonist drug class utilized in the treatment of psoriasis include:
  - Tremfya (guselkumab)
  - Stelara (ustekinumab)

#### Disease Background

Psoriasis affects 2% to 3% of the population, men and women equally.<sup>1</sup> Psoriasis commonly starts during a woman's reproductive years. The disease activity during pregnancy is unpredictable and, therefore, it is possible that treatment may be needed.<sup>2</sup> Based on limited safety data, current clinical guidelines for management of psoriasis during pregnancy and lactation recommend the following:

- First line: moisturizers and topical steroids (preferably low-medium potency)
- Second line: ultraviolet B phototherapy
- Third line: tumor necrosis factor inhibitors (adalimumab, etanercept, infliximab), cyclosporine, and systemic steroids.<sup>1,3</sup>

### REVIEW

#### Pregnancy

##### Nonclinical experience

As per the review by the Pharmacology/Toxicology reviewer, Jianyong Wang, Ph.D., the applicant has completed all the non-clinical studies to the Agency's satisfaction. An embryofetal developmental study conducted with tildrakizumab in pregnant cynomolgus monkeys revealed no treatment-related effects to the developing fetus when tildrakizumab was administered subcutaneously during

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<sup>1</sup> Bae Y, Van Voorhees A, Hsu S, et al. Review of treatment options for psoriasis in pregnant or lactating women: From the Medical Board of the National Psoriasis Foundation. J Am Acad Dermatol vol 67, Number 3:459-477.2012.

<sup>2</sup> Bangsgaard N, Rørbye C, Skov L et al. Treating Psoriasis During Pregnancy: Safety and Efficacy of Treatments. Am J Clin Dermatol. 2015 Jul 7. [Epub ahead of print]

<sup>3</sup> Zip C: A practical guide to dermatological drug use in pregnancy. Skin therapy letter 2006;11(4)1-4



organogenesis to near parturition at doses up to 159 times the maximum recommended human dose (MRHD). When dosing was continued until parturition, a small increase in neonatal death was observed at 59 times the MRHD. There were no concerns about humoral immunosuppression in the newborn monkeys' post in utero exposure to tildrakizumab. The clinical significance of this nonclinical finding is unknown.

#### Review of Literature

DPMH searched PubMed, Embase, ReproTox and TERIS databases for information regarding Ilumya (tildrakizumab) injection and use during pregnancy. No published information was identified. As per the applicant, no studies of Ilumya injection have been conducted in pregnant women.

#### Review of Clinical Trials

Because the drug has not yet been approved, no pharmacovigilance database has been established. Across the Ilumya for injection clinical development program, female subjects who were pregnant or lactating were excluded from enrollment in the clinical trials. However, 12 exposures during pregnancy with known outcomes and one pregnancy with an outcome pending have occurred across the clinical development program. Pregnancy outcomes included 6 cases of fetal loss (2 early spontaneous abortions occurring at 4 and 8 weeks of gestation in women exposed to Ilumya 200 mg and 4 elective abortions for personal reasons-no malformations were detected) and 6 full term normal live births; 1 pregnancy outcome is pending.

These limited clinical data are insufficient to draw meaningful safety conclusions about the effects of Ilumya during pregnancy and lactation.

#### Summary

Limited available data with Ilumya use in pregnant women are insufficient to inform a drug associated risk. Human IgG antibodies are known to cross the placental barrier; therefore, tildrakizumab may be transmitted from the mother to the developing fetus.

Intended and unintended exposures during pregnancy will likely occur because plaques psoriasis commonly occurs in females of reproductive potential. In addition, safety data regarding exposure during pregnancy are lacking because pregnant women were excluded during Ilumya clinical development program, and limited outcome data are available on the women who became pregnant in the clinical trials. Therefore, post-approval studies to assess outcomes following exposure in pregnancy are important to help characterize Ilumya safety in pregnancy. A pregnancy exposure registry is the Agency's preferred method for post-marketing data collection in pregnant women due to the prospective method of data collection, which minimizes the biases of retrospective data collection.<sup>4</sup> In addition, pregnancy registries provide for comparison with a control (comparator) group, which is preferable to pharmacovigilance data. However pregnancy registries are limited by their lack of power to assess specific (rare) birth defects and the long duration that may be needed to accumulate data. As discussed by the expert panel at the 2014 FDA public meeting on pregnancy registries and other post-approval safety studies in pregnant women, combining two study methods addresses limitations inherent to each study design.<sup>5</sup> Combining a pregnancy registry with a complementary study with a different study design that relies on large databases may address the potential low enrollment in a registry. Examples of complementary study designs include a retrospective cohort study using electronic medical record or claims data or a case control study.

DPMH recommends the following Post Marketing Requirement (PMR): "A prospective, registry based observational exposure cohort study that compares the maternal, fetal, and infant outcomes of women

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<sup>4</sup> FDA Guidance for Industry Establishing Pregnancy Exposure Registries

<sup>5</sup> FDA webpage Study Approaches and Methods To Evaluate the Safety of Drugs and Biological Products During Pregnancy in the Post-Approval Setting; Public Meeting <http://www.fda.gov/Drugs/NewsEvents/ucm386560.htm>

exposed to Ilumya during pregnancy to an unexposed control population” and an additional study “that uses a different study design (for example a retrospective cohort study using claims or electronic medical record data or a case control study) to assess major congenital malformations, spontaneous abortions, stillbirths, and small for gestational age in women exposed to Ilumya during pregnancy compared to an unexposed control population.” For more detailed description of the PMR, the reader is referred to the Appendix A.

## **Lactation**

### Nonclinical Experience

Low levels of tildrakizumab were detected in milk of cynomolgus monkeys in the pre- and postnatal developmental study. The mean tildrakizumab concentrations in milk were approximately 0.09 – 0.2% of that in serum on postpartum days 28 and 91.<sup>6</sup> While this informs that tildrakizumab will likely be present in human milk, due to species-specific differences in lactation physiology, these data cannot predict the tildrakizumab concentration levels in human milk. The clinical relevance of these data is not clear.

### Review of Literature

DPMH conducted a search of Medications and Mother’s Milk<sup>7</sup>, the Drugs and Lactation Database (LactMed)<sup>8</sup>, Micromedex<sup>9</sup>, and of published literature in PubMed using the search terms “tildrakizumab and lactation” and “tildrakizumab and breastfeeding.” No reports of clinical lactation studies or case reports of tildrakizumab use in lactating women were found in published literature.

The amounts of tildrakizumab transferred in breast milk are unlikely to result in systemic absorption in the infant because the molecule likely undergoes proteolysis in the stomach and intestine after ingestion. Nevertheless, local effects of exposure on the infant’s intestine cannot be excluded and merit further investigation.<sup>10,11,12</sup>

### Summary

Tildrakizumab has been detected in the milk of lactating cynomolgus monkeys; however, there are no data on the presence of tildrakizumab in human milk, the effects of the drug on the breastfed infant, or the effects of the drug on milk production. Maternal human IgG are present in breast milk in small amounts. Tildrakizumab, if transferred into breast milk, may be degraded in the gastrointestinal tract of the breastfeeding infant, however, its effects on the breastfed infant remain unknown. Therefore, DPMH recommends that the following risk/benefit statement is included in section 8.2 of labeling:

The development and health benefits of breastfeeding should be considered along with the mother’s clinical need for Ilumya and any potential adverse effects on the breastfed infant from Ilumya or from the underlying maternal condition.

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<sup>6</sup> Applicant’s proposed labeling edited by the Pharmacology/Toxicology reviewer

<sup>7</sup> Hale, Thomas (2015) Medications and Mothers’ Milk. Texas Hale Publishing

<sup>8</sup> <http://toxnet.nlm.nih.gov/cgi-bin/sis/htmlgen?LACT>. The LactMed database is a National Library of Medicine (NLM) database with information on drugs and lactation geared toward healthcare practitioners and nursing women. The LactMed database provides information when available on maternal levels in breast milk, infant blood levels, any potential effects in the breastfed infants if known, alternative drugs that can be considered and the American Academy of Pediatrics category indicating the level of compatibility of the drug with breastfeeding.

<sup>9</sup> Truven Health Analytics information, <http://www.micromedexsolutions.com/>.

<sup>10</sup> Ben-Horin S, Yavzori M, Kopylov U et al. Detection of infliximab in breast milk of nursing mothers with inflammatory bowel disease. J Crohns Colitis 2011;5:555–558.

<sup>11</sup> Ben-Horin S, Yavzori M, Katz L et al. Adalimumab level in breast milk of a nursing mother. Clin Gastroenterol Hepatol 2010;8:475–476

<sup>12</sup> Fritzsche J, Pilch A, Mury D et al. Infliximab and adalimumab use during breastfeeding. J Clin Gastroenterol 2012;46:718–

## **Females and Males of Reproductive Potential**

### Nonclinical Experience

No effects on fertility parameters were observed in male or female cynomolgus monkeys that were administered tildrakizumab at subcutaneous or intravenous doses up to 140 mg/kg once every two weeks for 3 months (133 or 155 times the MRHD, respectively, based on AUC comparison). The monkeys were not mated to evaluate fertility.

### Review of Literature

DPMH performed a search of published literature on tildrakizumab and infertility and did not identify any publications.

### Summary

Animal reproductive studies of administration of tildrakizumab did not show any adverse effects on fertility. Since there are no human data available on the effect of tildrakizumab on fertility, and neither need for contraception nor pregnancy testing exists, Subsection 8.3, Females and Males of Reproductive Potential, will not be included in Ilumya labeling.

## **CONCLUSION**

The Pregnancy and Lactation, sections of Ilumya labeling were structured to be consistent with the PLLR as follows:

- **Pregnancy, Subsection 8.1**
  - The “Pregnancy” subsection of Ilumya labeling was formatted in the PLLR format to include: “Pregnancy Exposure Registry,” “Risk Summary,” and “Data” headings.
- **Lactation, Subsection 8.2**
  - The “Lactation” subsection of Ilumya labeling was formatted in the PLLR format to include the “Risk Summary” and “Data” headings.
- **Patient Counseling Information, Section 17**
  - The “Patient Counseling Information” section of labeling was updated to include the Pregnancy Exposure Registry

## **RECOMMENDATIONS**

1.) DPMH participated in a labeling meeting with DDDP on October 11, 2017 and October 24, 2017. DPMH revised subsections 8.1 and 8.2 and section 17 of the Ilumya labeling for compliance with the PLLR. DPMH refers to the final BLA action for final labeling.

2.) DPMH proposes a Post-Marketing Requirement that requires the applicant to perform a pregnancy exposure registry study and a complementary study to assess the safety of Ilumya in pregnant women. The language for the PMR is included in Appendix A. Further discussions at this time between the Division and the applicant continue in order to streamline the pregnancy exposure registry to ensure it meets the requirements of the PMR.

# DPMH PROPOSED PREGNANCY AND LACTATION LABELING EDITS FOR ILUMYA

## FULL PRESCRIBING INFORMATION

### 8 USE IN SPECIFIC POPULATIONS

#### 8.1 Pregnancy

##### Pregnancy Exposure Registry

There is a pregnancy exposure registry that monitors pregnancy outcomes in women exposed to Ilumya during pregnancy. For more information contact (Applicant to provide information/telephone number and web page).

##### Risk Summary

The available data from case reports on ILUMYA use in pregnant women are insufficient to inform a drug associated risk of adverse developmental outcomes. Human IgG is known to cross the placental barrier; therefore, ILUMYA may be transferred from the mother to the fetus. An embryofetal developmental study conducted with tildrakizumab in pregnant monkeys revealed no treatment-related effects to the developing fetus when tildrakizumab was administered subcutaneously during organogenesis to near parturition at doses up to 159 times the maximum recommended human dose (MRHD). When dosing was continued until parturition, a small increase in neonatal death was observed at 59 times the MRHD (*see Data*). The clinical significance of this nonclinical finding is unknown.

All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. The background risk of major birth defects and miscarriage for the indicated population is unknown. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.

##### Data

##### *Animal Data*

In an embryofetal developmental study, subcutaneous doses up to 300 mg/kg tildrakizumab were administered to pregnant cynomolgus monkeys once every two weeks during organogenesis to gestation day 118 (22 days from parturition). No maternal or embryofetal toxicities were observed at doses up to 300 mg/kg (159 times the MRHD of 100 mg, based on AUC comparison). Tildrakizumab crossed the placenta in monkeys.

In a pre- and postnatal developmental study, subcutaneous doses up to 100 mg/kg tildrakizumab were administered to pregnant cynomolgus monkeys once every two weeks from gestation day 50 to parturition. Neonatal deaths occurred in the offspring of one control monkey, two monkeys at 10 mg/kg dose (6 times the MRHD based on AUC comparison), and four monkeys at 100 mg/kg dose (59 times the MRHD based on AUC comparison). The clinical significance of these nonclinical findings is unknown. No tildrakizumab-related adverse effects were noted in the remaining infants from birth through 6 months of age.

#### 8.2 Lactation

##### Risk Summary

There are no data on the presence of tildrakizumab in human milk, the effects on the breastfed infant, or the effects on milk production. Human IgG is known to be present in human milk. Tildrakizumab was

detected in the milk of monkeys. When a drug is present in animal milk, it is possible that the drug will be present in human milk.

The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for ILUMYA and any potential adverse effects on the breastfed child from ILUMYA or from the underlying maternal condition.

## **17 PATIENT COUNSELING INFORMATION**

### Pregnancy Exposure Registry

Advise patients that there is a pregnancy exposure registry that monitors pregnancy outcomes in women exposed to ILUMYA during pregnancy [*see Use in Specific Populations (8.1)*].

## **APPENDIX A: DPMH PMR LANGUAGE FOR ILUMYA PREGNANCY EXPOSURE REGISTRY**

DPMH recommends the following PMR language:

FDA has determined that you are required to conduct the following post-approval safety studies in pregnant women:

*“A prospective, registry based observational exposure cohort study that compares the maternal, fetal, and infant outcomes of women exposed to Ilumya during pregnancy to an unexposed control population. The registry will detect and record major and minor congenital malformations, spontaneous abortions, stillbirths, elective terminations, small for gestational age, 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.*

*And*

*An additional study that uses a different study design (for example a retrospective cohort study using claims or electronic medical record data or a case control study) to assess major congenital malformations, spontaneous abortions, stillbirths, and small for gestational age in women exposed to Ilumya during pregnancy compared to an unexposed control population.”*

For guidance on how to establish a pregnancy exposure registry, the applicant should review the Guidance for Industry on Establishing Pregnancy Exposure Registries available at <http://www.fda.gov/cder/guidance/3626fnl.htm>. For information on complementary study methods, the applicant should review the FDA webpage Study Approaches and Methods To Evaluate the Safety of Drugs and Biological Products During Pregnancy in the Post-Approval Setting; Public Meeting <http://www.fda.gov/Drugs/NewsEvents/ucm386560.htm>.

Draft study protocols should be submitted three months after product approval.

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/s/  
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CHRISTOS MASTROYANNIS  
12/21/2017

LYNNE P YAO  
12/21/2017

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## **HUMAN FACTORS, LABEL, LABELING, AND PACKAGING 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\*\*\***

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<b>Date of This Review:</b>	November 21, 2017
<b>Requesting Office or Division:</b>	Division of Dermatology and Dental Products (DDDP)
<b>Application Type and Number:</b>	BLA 761067
<b>Product Name and Strength:</b>	Ilumya (tildrakizumab) Injection, 100 mg/mL
<b>Product Type:</b>	Single Ingredient Combination Product
<b>Rx or OTC:</b>	Rx
<b>Applicant/Sponsor Name:</b>	Merck Sharp and Dohme Corp.
<b>Submission Date:</b>	March 23, 2017
<b>OSE RCM #:</b>	2017-607 and 2017-846
<b>DMEPA Safety Evaluator:</b>	Carlos M Mena-Grillasca, BS Pharm
<b>DMEPA Team Leader:</b>	Sarah K. Vee, PharmD
<b>DMEPA Associate Director for Human Factors:</b>	QuynhNhu Nguyen, MS

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## 1 REASON FOR REVIEW

This review evaluates the proposed container label, carton labeling, Prescribing Information (PI), and Instructions for Use (IFU) for Ilumya (tildrakizumab) injection (BLA 761066), in response to consults from the Division of Dermatology and Dental Products (DDDP). The Applicant submitted BLA 761067, a 351(a) application, on March 23, 2017 for a prefilled syringe containing Ilumya (tildrakizumab).

## 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.

<b>Table 1. Materials Considered for this Label and Labeling Review</b>		
<b>Material Reviewed</b>	<b>Appendix Section (for Methods and Results)</b>	
Product Information/Prescribing Information	A	
Previous DMEPA Reviews	B	
Human Factors Study	C – N/A	
ISMP Newsletters	D – N/A	
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 our label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

## 3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

### Human Factors

Merck Sharp & Dohme submitted BLA 761067 as a 351(a) application on March 23, 2017 for the treatment of adults with moderate-to-severe plaque psoriasis who are candidates for systemic therapy or phototherapy. The proposed commercial product is a 100 mg/mL prefilled syringe (PFS) with safety needle guard.

DMEPA reviewed the Human Factors (HF) protocol, use-related risk analysis (URRA), and Instructions for Use (IFU) submitted by the Sponsor to IND 101389 on October 28, 2015<sup>a</sup>, November 13, 2015<sup>b</sup>, and December 14, 2015<sup>c</sup>. Within the March 8, 2016 Advice/Information Request letter<sup>d</sup> we advised the Sponsor that “As your proposed prefilled syringe is similar to other marketed products, provide justification for the need for a human factors study in the proposed patient population and discuss differences between your proposed prefilled syringe compared to those currently marketed. If you decide to conduct human factors study, we recommend you implement the following recommendation...”. The Sponsor subsequently responded to the Advice/Information Request letter stating that based on our advice they would not pursue a Human Factors validation study<sup>e</sup>.

<sup>a</sup> Available from: <\\cdsesub1\evsprod\ind101389\0199\m1\us\quality-information-amendment-28oct2015.pdf>

<sup>b</sup> Available from: <\\cdsesub1\evsprod\ind101389\0201\m3\32-body-data\32p-drug-prod\mk-3222-solution-for-injection-solution-for-injection\32p2-pharm-dev\pharmaceutical-development.pdf>

<sup>c</sup> Available from: <\\cdsesub1\evsprod\ind101389\0206\m1\us\multiple-module-information-amendment-11dec2015-1.pdf>

<sup>d</sup> Marcus, K. Advice/Information Request Letter for Tildrakizumab. Silver Spring (MD): FDA, CDER, OND, DDDP (US); 2016 MAR 08. IND 101389.

<sup>e</sup> Available from: <\\cdsesub1\evsprod\ind101389\0213\m1\us\multi-module-info-amendment-11apr2016.pdf>

Subsequently, the Applicant submitted a summary of the Human Factors formative studies and revised use-related risk analysis to the original BLA<sup>a</sup>. In addition, Merck indicated that the proposed prefilled syringe is the same as the currently marketed Cosentyx PFS. Also, (b) (4) the Dosage and Administration section of the Prescribing Information indicates "Ilumya should only be administered by healthcare providers".

### Labels and Labeling

Our review of the proposed container labels and carton labeling noted areas for improvement. The container label should include a linear bar code per 21 CFR 201.25(b)(2). The route of administration statement "For subcutaneous use" on the carton labeling can be improved by increasing the prominence and relocating below the strength statement. The labels and labeling should be revised to include the proposed, conditionally acceptable proprietary name Ilumya.

Our recommendations to improve the container labels and carton labeling are provided in Section 4.1.

## **4 CONCLUSION & RECOMMENDATIONS**

We agree with Merck's use related-risk analysis and note that the URRA did not identify any new or unique risks for use with this product. In addition, (b) (4) (b) (4), we concur that no additional human factors validation data are needed to support the PFS presentation.

Our review of the proposed container labels and carton labeling identified areas for improvement. We provide recommendations for Merck Sharp & Dohme in Section 4.1. We recommend the following be implemented prior to approval of this BLA.

### **4.1 RECOMMENDATIONS FOR MERCK SHARP & DOHME**

- A. General Recommendations (All labels and labeling)
  - 1. Your proposed proprietary name Ilumya was found conditionally acceptable. Therefore, revise the proprietary name placeholder from 'Trademark' to read 'Ilumya'.
  - 2. Ensure the proper name is at least half the size of the proprietary name on all instances where it is presented on the container labels and carton labeling in accordance with 21 CFR 201.10(g)(2).
- B. Container Labels (trade and sample)
  - 1. Delete (b) (4) presented above the lot number as it is prominently displayed on the label and it is non-sensical to healthcare providers and patients and may be confused for a lot number or NDC number. If this is a placeholder for an internal item code, consider relocating to the side of the label.
  - 2. Per 21 CFR 201.25(b)(2), include a bar code and ensure there is adequate white space around the linear bar code to facilitate scanning.
- C. Carton Labeling (trade and sample)
  - 1. Increase the prominence of the route of administration statement 'For Subcutaneous Use Only' by bolding and/or using a color font and relocate below the strength statement.

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<sup>a</sup> Available from: <\\cdsesub1\evsprod\bla761067\0000\m5\53-clin-stud-rep\535-rep-effic-safety-stud\psoriasis\5354-other-stud-rep\04m86w\04m86w.pdf>

## APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

### APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Ilumya that Merck Sharp & Dohme submitted on March 23, 2017.

Table 2. Relevant Product Information for Ilumya	
Initial Approval Date	N/A
Active Ingredient	tildrakizumab
Indication	Treatment of adults with moderate-to-severe plaque psoriasis who are candidates for systemic therapy or phototherapy
Route of Administration	Subcutaneous
Dosage Form	Injection
Strength	100 mg/mL
Dose and Frequency	100 mg at weeks 0, 4, and every 12 weeks thereafter
How Supplied	100 mg/mL Pre-filled syringe in cartons of 1 unit
Storage	Refrigerated at 2°C to 8°C (36°F to 46°F)
Container Closure	Pre-filled syringe with safety needle guard

### APPENDIX B. PREVIOUS DMEPA REVIEWS

On November 8, 2017, we searched DMEPA's previous reviews using the terms, tildrakizumab and Ilumya. Our search identified one previous relevant review<sup>a</sup>, and we confirmed that our previous recommendations were implemented or considered.

### APPENDIX C. HUMAN FACTORS STUDY

N/A

### APPENDIX D. ISMP NEWSLETTERS

N/A

### APPENDIX E. FDA ADVERSE EVENT REPORTING SYSTEM (FAERS)

N/A

### APPENDIX F. OTHER SOURCES

N/A

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<sup>a</sup> Mehta, H. Human Factors Protocol Review for Tildrakizumab IND 101389. Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2016 JAN 14. RCM No.: 2015-2479.

## **APPENDIX G. LABELS AND LABELING**

### **G.1 List of Labels and Labeling Reviewed**

Using the principles of human factors and Failure Mode and Effects Analysis,<sup>a</sup> along with postmarket medication error data, we reviewed the following Ilumya labels and labeling submitted by Merck Sharp & Dohme on March 23, 2017.

- Container label
- Carton labeling
- Prescribing Information (Image not shown)

### **G.2 Label and Labeling Images**

Proposed Container Labels (not to scale)

(b) (4)



3 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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<sup>a</sup> Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

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/s/  
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CARLOS M MENA-GRILLASCA  
11/21/2017

SARAH K VEE  
11/22/2017

QUYNH NHU T NGUYEN  
11/22/2017



# Memorandum

DEPARTMENT OF HEALTH AND HUMAN SERVICES  
PUBLIC HEALTH SERVICE  
FOOD AND DRUG ADMINISTRATION  
CENTER FOR DRUG EVALUATION AND RESEARCH  
DIVISION OF CARDIOVASCULAR AND RENAL PRODUCTS

Date: 25 September, 2017

From: Fred Senatore, MD, PhD, FACC  
Clinical Reviewer  
Division of Cardiovascular and Renal Products / CDER

Through: Martin Rose, MD, JD, Team Leader  
Norman Stockbridge, MD, PhD, Division Director  
Division of Cardiovascular and Renal Products / CDER

To: Kevin Clark, Clinical Reviewer, DDDP  
Gordana Diglisic, CDTL, DDDP

Subject: Review CV events in BLA 761067 and provide recommendations regarding appropriate language for labeling.

This memo responds to your consult to us requesting our review of major adverse cardiovascular events (MACE) from BLA 761067 supporting tildrakizumab, a humanized IgG1/k monoclonal antibody targeting interleukin-23 for the treatment of moderate to severe plaque psoriasis in patients who are candidates for systemic therapy or phototherapy.

DCRP received and reviewed the following materials:

- Your consult request dated 31 March 2017 but received 29 August 2017.

I retrieved BLA 761067 (<file:///CDSESUB1/evsprod/BLA761067/761067.enx>) in DARRTS and reviewed the Clinical Overview, Summary of Clinical Efficacy, Summary of Clinical Safety, the CSRs of the Phase 2 and two Phase 3 trials forming the basis of the BLA, and Integrated Summary of Safety (ISS).

## Background

Merck Sharp & Dohme (MSD) submitted BLA 761067 to support tildrakizumab for the treatment of psoriasis. Concerns were raised by a numerical excess of MACE (i.e., myocardial infarction, stroke, and cardiovascular death) when treating patients with chronic plaque psoriasis with antibodies to interleukin-12 (IL-12) and interleukin-23 (IL-23). However, studies evaluating the effect of these agents on MACE showed mixed results and may have been inconclusive. One study of 5 randomized clinical trials (n=4700 patients) evaluating ustekinumab and briakinumab detected a statistically significant increase in MACE when using the Peto method (p=0.04), but the significance was lost when using the Mantel-Haenszel fixed effects model (Tzellos, 2012). The authors concluded that an anti-interleukin 12/23 class effect of increasing MACE could not be excluded, and that patients with chronic plaque psoriasis should be screened for manageable cardiovascular risk factors before initiating anti-IL12/23 agents. Another study of 22 randomized clinical trials (n=10,000 patients) evaluating ustekinumab, briakinumab, adalimumab, etanercept, and infliximab showed no significant difference between anti-IL12/23 therapies and placebo for MACE (Ryan, 2011). The authors felt, however, that the study may have been underpowered to identify a significant difference. Based on these mixed and inconclusive results from the literature, MSD conducted an analysis of MACE in their program. In this consult, we reviewed Merck's MACE analysis and independently evaluated the MACE data.

## Tildrakizumab Clinical Development

The development program consisted of:

- Phase 1: Six trials. Three trials were conducted in healthy subjects (P05661, P05776, and P06306); two trials were in subjects with psoriasis (P05382 and Protocol 009) ; and one trial was conducted in subjects with Crohn's Disease (P05839).
- Phase 2: One dose-ranging trial was completed in subjects with moderate-severe chronic plaque psoriasis (P05495).
- Phase 3: Two trials. Each trial was multiple-dose (Protocol 010 and Protocol 011) in subjects with moderate to severe chronic plaque psoriasis.

The BLA included efficacy and safety data from P05495, P010 and P011 as well as supportive evaluation of PK, PD, and safety from Phase 1 studies. A summary of the designs and number of subjects randomized in each arm of P05495, P010 and P011 from which cardiac events were analyzed are shown in [Table 1](#).

The Phase-2 P05495 study was a 52-week randomized double-blind, placebo controlled, parallel-group, dose-range finding trial. Subjects were randomized to receive one of four doses of tildrakizumab SQ administered every 4 weeks: 5, 25, 100, and 200 mg. The study was divided into Part 1 (Week 0 to 16) and Part 2 (Week 16 to 52). At the end of Part 1, treatment assignments were maintained or modified in blinded fashion based on the Psoriasis Area Severity Index (PASI) response. At the end of Part 2, drug was discontinued and each subject continued under observation with monthly assessment through Week 72 (Part 3).

The Phase-3 P010 study was a 64-week randomized double-blind, placebo controlled, parallel-group trial with a long term safety extension. Subjects were randomized to receive SC doses of either placebo, tildrakizumab 100 mg, or tildrakizumab 200 mg administered every 4 weeks. The trial consisted of three parts. Part 1 was a 12-week randomized double-blind placebo-controlled period to evaluate initial treatment response (Weeks 0 to 12). Part 2 was a 16-week randomized double-blind period to evaluate maintenance of response (Weeks 12 to 28). In Part 2, subjects who were randomized to placebo were re-randomized to either tildrakizumab 100 mg or 200 mg. Part 3 was a 36-week double-blind treatment period to evaluate long-term efficacy and safety (Weeks 28 to 64). In Part 3, subjects were re-randomized to either tildrakizumab 100 mg or 200 mg or placebo depending on whether there was a complete or partial response (as determined by PASI) and also depending on which tildrakizumab dose the subjects were originally randomized to. Those subjects originally randomized to tildrakizumab 100 mg or 200 mg subsequently classified as non-responders were eliminated. Following Part 3, there was an elective long-term safety extension for approximately 192 weeks. The design is illustrated in [Appendix 1-P010 Trial Design](#) of this review.

The Phase-3 P011 study was a 52-week randomized double-blind active comparator and placebo-controlled parallel group trial with a long term safety extension. Subjects were randomized to receive SC doses of either placebo, tildrakizumab 100 mg, or tildrakizumab 200 mg administered every 4 weeks. Etanercept (50 mg SC twice weekly accompanied by an etanercept placebo) served as the active comparator control. As in the P010 trial, the P011 trial consisted of three parts. Part 1 was a 12-week randomized double-blind placebo-controlled period to evaluate initial treatment response (Weeks 0 to 12). Part 2 was a 16-week randomized double-blind treatment period to evaluate the maintenance of response (Weeks 12 to 28). In Part 2, subjects who were randomized to placebo were re-randomized to either tildrakizumab 100 mg or 200 mg. Part 3 was a 24-week double-blind treatment period to evaluate long-term efficacy and safety (Weeks 28 to 52). In Part 3, subjects were re-randomized to either tildrakizumab 100 mg or 200 mg (placebo not involved) depending on whether there was a complete or partial response



(as determined by PASI) and also depending on which tildrakizumab dose the subjects were originally randomized to. Non-responders were eliminated. Subjects on etanercept who responded were also eliminated. Non-responders or partial responders on etanercept were placed on tildrakizumab 200 mg (not clear if blinded). Following Part 3, there was an elective long-term safety extension for approximately 192 weeks. The design is illustrated in [Appendix 2-P011 Trial Design](#) of this review.

A total of 2217 subjects were randomized in the Phase 2 and the two Phase 3 trials. Of the subjects randomized, 357 subjects were randomized to placebo, 705 subjects to tildrakizumab 100 mg, 708 subjects to tildrakizumab 200 mg, and 313 subjects to etanercept 50 mg. All others were randomized to tildrakizumab 5 mg or 25 mg.

A total of 1862 subjects were randomized in the two Phase-3 trials: 311 subjects to placebo, 616 to tildrakizumab 100 mg, 622 to tildrakizumab 200 mg, and 313 to etanercept 50 mg.

The extent of exposure is shown in [Table 2](#). The numbers in this table represent any randomized subject who received any dose of tildrakizumab. Initial doses were counted as 4 weeks of exposure. Subsequent doses from re-randomizations were counted as 12 weeks. Subjects who took more than 1 treatment either by changing doses between trial parts or by changing from placebo to tildrakizumab was counted according to the time spent in each dose. Most of the subjects took the therapeutic dose of 100 mg or 200 mg for a mean duration 48 or 47 weeks, respectively.

**Table 1: Summary of Efficacy Trials Supporting BLA 761067**

Protocol Number	Trial Design	Number Randomized/Arm
<i>Phase 2 trial</i>		
P05495	Randomized, double-blind, placebo controlled, parallel-group, dose-range finding trial	Tildrakizumab 5 mg: 42 Tildrakizumab 25 mg: 92 Tildrakizumab 100 mg: 89 Tildrakizumab 200 mg: 86 Placebo: 46 Total: 355
<i>Phase 3 trials</i>		
P010	Randomized, double-blind, placebo controlled, parallel-group trial with long term safety extension	Tildrakizumab 100 mg: 309 Tildrakizumab 200 mg: 308 Placebo: 155 Total: 772
P011	Randomized, double-blind, active comparator and placebo controlled, parallel-group trial with long term safety extension	Tildrakizumab 100 mg: 307 Tildrakizumab 200 mg: 314 Etanercept: 313 Placebo: 156 Total: 1090

Source: Module 2.7.3 Summary of Clinical Efficacy

**Table 2: Extent of Exposure to tildrakizumab (Drug)**

Drug	>0 to<12 weeks	≥ 12 to <28 weeks	≥ 28 to <52 weeks	≥ 52 to <64 weeks	≥ 64 weeks	Mean Duration (weeks)
Any Dose	32	72	499	223	1168	54
5 mg	2	27	3	0	10	28
25 mg	3	28	34	1	57	47
100 mg	6	122	413	98	44	48
200 mg	21	81	423	106	410	47

Source: Module 2.5 Clinical Overview [ISS: analysis-ads]

## Evaluation of Cardiac Events

External Data Safety Monitoring Boards were responsible for adjudicating cardiac events for the Phase 2 study (P05495) and the Phase 3 studies (P010 and P011).

The Adjudication committee assessed the cardiovascular events using three definitions:

- MACE: defined as nonfatal myocardial infarction, nonfatal stroke, and cardiovascular deaths that were confirmed as “cardiovascular” or “sudden”.
- Extended MACE: defined as MACE, unstable angina, coronary revascularization, and resuscitated cardiac arrest.
- Fatal and nonfatal thrombotic / embolic / ischemic events: included MACE, extended MACE, transient ischemic attack, pulmonary embolism, peripheral arterial thrombosis / thromboembolism, and venous thrombosis.

For this evaluation I focused on MACE as defined in the Applicant’s package for 3 reasons:

1. This is the standard biologically driven endpoint normally used to evaluate cardiovascular risk or cardiovascular efficacy.
2. Coronary revascularization as a component of extended MACE is not characteristically accepted as an endpoint because it is investigator driven and potentially subjective.

3. The data from the Applicant's ISS and the summary of clinical safety suggest that MACE events, based on their ischemic / thrombotic etiology, were also adjudicated as thrombotic-embolic-ischemic events. The category of thrombotic-embolic-ischemic events was therefore a duplicate adjudication for MACE. Two events that were adjudicated to be thrombotic-embolic-ischemic events but not MACE were deep venous thrombosis and mesenteric artery thrombosis. These two events are generally not considered to be a cardiac event in cardiovascular trials.

The evaluation of adverse events was based on the strategy underlying the ISS (section 1.1.1 ISS):

- Phase 2 and Phase 3 placebo-controlled safety pool: used to make comparisons between tildrakizumab and placebo over the placebo-controlled period (16 weeks for P05495 and 12 weeks for P010 and P011). Data were pooled across trials and treatment groups and were presented as follows: placebo, tildrakizumab 100 mg, tildrakizumab 200 mg, combined tildrakizumab (100mg/200mg), and etanercept 50 mg (active comparator control in the P011 study only).
- Phase 3 controlled safety pool: used to make comparisons between tildrakizumab and placebo over the 12 week placebo-controlled period in the Phase 3 trials only. Data were pooled across trials and treatment groups were presented as follows: placebo, tildrakizumab 100 mg, tildrakizumab 200 mg, combined tildrakizumab (100mg/200mg), and etanercept 50 mg (active comparator control in the P011 study only).
- Phase 2 and 3 base period safety pool: used to support exposure-adjusted summary of adverse events. This pool included Phase 2 and Phase 3 "base" periods (52 weeks for the Phase 2 and P011 trials, and 64 weeks for the P010 trial). Data were pooled across trials and treatment groups and were presented as follows: placebo, tildrakizumab 100 mg, continuous exposure tildrakizumab 100 mg, tildrakizumab 200 mg, continuous exposure tildrakizumab 200 mg, combined tildrakizumab (100 mg/200 mg), continuous exposure combined tildrakizumab (100 mg/200 mg), and etanercept 50 mg (active comparator control in the P011 study only).
- Phase 3 extension safety pool: used to assess long-term safety and tolerability of tildrakizumab.

There was a paucity of events adjudicated as MACE. I felt the ISS strategy involving multiple cuts of the database was too complex for the small number of MACE. I

therefore reviewed the adverse event data directly from the three pivotal trials (Phase 2 P05495, Phase 3 P010, and Phase 3 P011).

There was no adjudicated MACE in the Phase 2 trial. The number of subjects with adjudicated MACE from the pooled sample size of the Phase 2 / Phase 3 database for each arm is shown in Table 3. There were 6 adjudicated MACE. One subject had an adjudicated event while on placebo (b) (6) (ischemic stroke). Three subjects had an adjudicated event while on tildrakizumab 100 mg (b) (6), NSTEMI; (b) (6), CV Death; (b) (6), CV Death), and two subjects had an adjudicated event while on tildrakizumab 200 mg ((b) (6), CV Death; (b) (6), Ischemic stroke). There were no MACE in the etanercept 50 mg arm. A description of each subject experiencing a MACE is shown in Table 4 for the Phase 3 trial P010 and in Table 5 for the Phase 3 trial P011. Observations from these two tables were:

- All subjects had the MACE after drug was discontinued.
- One subject in the P010 trial (none in the P011 trial) had a MACE during the 12-week double blind part ((b) (6) on tildrakizumab 100 mg). The remainder of the subjects had adjudicated events in Part 3.
- All the subjects had cardiovascular risk factors.

In the extension period of the Phase 3 studies, there were 5 subjects (4 in the tildrakizumab 100 mg arm and 1 in the tildrakizumab 200 mg arm) who had an adjudicated MACE as shown in Table 6. A description of each subject experiencing a MACE in the extension period is shown in Table 7. There were no deaths. Three subjects had a stroke ((b) (6)); one subject had a non-ST segment elevation myocardial infarction (NSTEMI) following an episode of unstable angina (b) (6); and one subject had an out-of-hospital cardiac arrest secondary to ventricular fibrillation and acute myocardial infarction (b) (6). Two of the stroke subjects discontinued tildrakizumab prior to the adverse events (i.e., subject (b) (6): 100 mg dosing discontinued 20 days prior to the ischemic lacunar infarct; subject (b) (6): 100 mg dosing discontinued 111 days prior to the hemorrhagic stroke). The other three subjects continued tildrakizumab after resolution of the MACE.

**Table 3: Adjudicated MACE from pooled Phase 2 and Phase 3 Trials**

	Placebo	Tildrakizumab 100 mg	Tildrakizumab 200 mg	Etanercept 50 mg
	N (%)	N (%)	N (%)	N (%)
Subjects who took at least one dose of study drug	355	705	708	313
MACE	1 (0.3%)	3 (0.4%)	2 (0.3%)	0 (0.0%)

Source: Reviewer Compilation of P010 and P011 CSRs-Safety Database

**Table 4: Subjects in Study P010 with an adjudicated MACE**

<b>Subject ID</b>	<b>Treatment</b>	<b>CRF</b>	<b>Adjudicated MACE</b>	<b>Event Date</b>	<b>Outcome</b>
(b) (6) 42 y/o WM	T 100 mg and re-randomized to Pbo Part 3	12-pk years	Ischemic CVA	Day 397- last dose day 112	Resolved Day 415 with sequelae. Withdrew from study Day 427
(b) (6) 55 y/o biracial M	T 200 mg and remained on dose	HTN, 20-pk years	CV Death	Day 411- last dose Day 365	Cardiac arrest during peripheral vascular bypass surgery-died
(b) (6) 62 y/o WM	Pbo and re- randomized to T 200 mg in Part 2 and continued on 200 mg	DM, high LDL, hx CABG, HTN, smoking	Ischemic CVA	Day 449- last dose Day 456	Resolved Day 454 and continued into extension
(b) (6) 42 y/o BM	T 100 mg and remained on dose	HTN, 5 pk- year, high cholesterol	Acute MI (NSTEMI) / PCI	Day 67- last dose Day 30	Resolved Day 68 s/p stent. Discontinued Day 86 2° cannabis use

Source: P010 CSR, Section 14.3.4.3.1; CRF=Cardiac Risk Factors; T=tildrakizumab

**Table 5: Subjects in Study P011 with an adjudicated MACE**

<b>Subject ID</b>	<b>Treatment</b>	<b>CRF</b>	<b>Adjudicated MACE</b>	<b>Event Date</b>	<b>Outcome</b>
(b) (6) 74 y/o Asian Male	T 100 mg and remained on dose	High cholesterol, HTN	CV Death	Day 290-last dose Day 282	Death due to acute MI
(b) (6) 48 y/o WM	T 100 mg and remained on dose	Dyslipidemia, hyperuricemia, obesity, HTN	MI/out-of-hospital cardiac arrest/death	Day 376-last dose Day 284-completd study Day 360 but did not enter extension	Unsuccessful resuscitation at home, no more exam, no autopsy

Source: P011 CSR, Section 14.3.2.3.1; CRF=Cardiac Risk Factors; T=tildrakizumab; E=etanercept

**Table 6: Adjudicated MACE from Phase 3 Extension Safety Pool**

<b>Tildrakizumab Dose</b>	<b>100 mg</b>	<b>200 mg</b>
# Subjects in extension	621	616
MACE	4 (0.6%)	1 (0.2%)

Source: Module 2.7.4 Summary of Clinical Safety, ISS-EXT: analysis-adsl, adae



**Table 7: Subjects in the pooled Phase 3 extension trials with an adjudicated MACE**

Subject ID	Treatment	CRF	Adjudicated MACE	Event Date	Outcome
(b) (6) 59 y/o Asian male	T 100 mg and remained on dose	HTN, right hemiplegia, polycythemia,	Hemorrhagic stroke	Day 561- last dose Day 450	Resolved with sequelae Day 632, withdrew from the study Day 450
(b) (6) 57 y/o Asian male	Pbo and rerandomized to T 100 mg in Part 2 and continued on 100 mg	HTN, 35-pk years	Non-fatal ischemic stroke	Day 741	Resolved Day 775 with sequelae-continued treatment
(b) (6) 52 y/o WM	T 200 mg and remained on dose	Ex-smoker (3 packs /year) unknown number of years	Resuscitated cardiac arrest, non-fatal acute MI, PCI	Day 470	Resolved Day 521-continued treatment
(b) (6) 46 y/o multi-racial male	Pbo and re-randomized to T 100 mg on Day 86, continued on this dose into extension	Ex-smoker (1 pack/week) unknown number of years, obesity (BMI 34), PFO	Lacunar infarct	Day 560- last dose Day 540	Resolved Day 568
(b) (6) 66 y/o white male	T 100 mg and remained on the dose	HTN	NSTEMI	Day 769	Resolved Day 775-continued treatment

Source: Summary of Clinical Safety, module 2.7.4, page 153 derived from CIOMS reports, Module 5.3.5.3.2.2

## DRCP Assessment

There was a low incidence of MACE (0.3%-0.4%) in the base period of the trials over a mean of 48 weeks which approximates the annualized incidence. Similarly, the MACE rate in the extension period was low (0.4% over 89 weeks) derived by averaging the event rates from [Table 6](#) and averaging the event dates from [Table 7](#). The estimated annualized event rate from this calculation was 0.2%/year.

The MACE data from this study was compared to a cohort study that evaluated the association between psoriasis and the risk of MACE that was defined as the composite

of myocardial infarction, acute coronary syndrome, unstable angina, and stroke (Parisi, 2015).

*Reviewer Comment: Unstable angina is defined as acute coronary syndrome as well as myocardial infarction.*

Using the Clinical Practice Research Datalink, 48,523 patients with psoriasis and 208,187 controls were included in this evaluation. During a median follow-up of 5.2 years, 1,257 patients with psoriasis (2.59%) had a major cardiovascular event, compared with 4,784 controls (2.30%). The annual rates were therefore estimated to be 0.5% for patients with psoriasis and 0.4% for controls.

The incidence of MACE from the Phase 3 trials supporting tildrakizumab was similar to that derived from the Clinical Practice Research Link for both patients with psoriasis and corresponding controls.

In conclusion, the incidence of adjudicated MACE evaluated from the Phase 2 / Phase 3 pooled database was low and similar to that derived from a large database, thereby precluding a clinical concern.

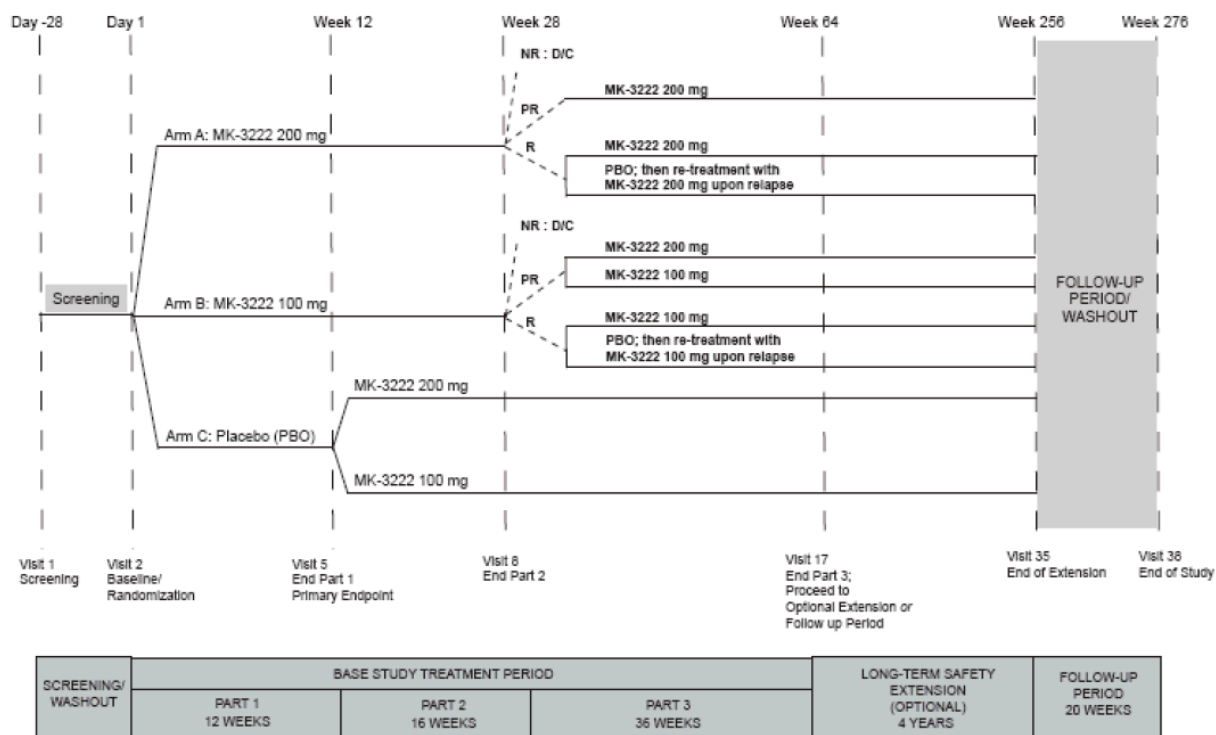
## References

Parisi, R, et al., 2015, psoriasis and risk of major cardiovascular events: cohort study using the clinical practice research datalink, J Invest Dermatol, Sep, 135 (9): 2189-2197

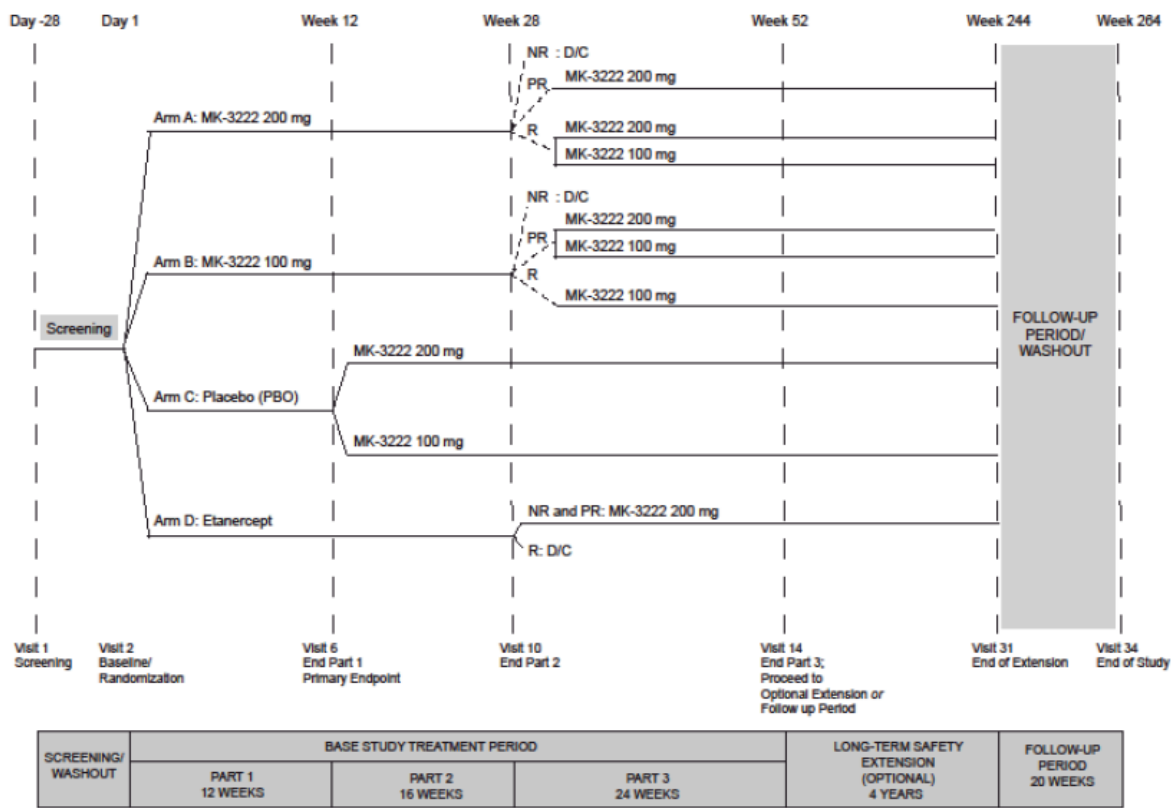
Ryan, C, et al., 2011, association between biologic therapies for chronic plaque psoriasis and cardiovascular events: a meta-analysis of randomized controlled trials, JAMA, 306 (8): 864-871

Tzellos, T, et al., 2012, association of ustekinumab and briakinumab with major adverse cardiac events, Dermato-Endocrinology, 4:3, 320-323

# Appendix 1-P010 Trial Design



# Appendix 2-P011 Trial Design



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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.**  
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/s/  
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FORTUNATO F SENATORE  
09/29/2017

MARTIN ROSE  
09/29/2017

NORMAN L STOCKBRIDGE  
10/01/2017



# Memorandum

DEPARTMENT OF HEALTH AND HUMAN SERVICES  
PUBLIC HEALTH SERVICE  
FOOD AND DRUG ADMINISTRATION  
CENTER FOR DRUG EVALUATION AND RESEARCH  
DIVISION OF CARDIOVASCULAR AND RENAL PRODUCTS

Date: September 29, 2017

From: CDER DCRP QT Interdisciplinary Review Team

Through: Christine Garnett, Pharm.D.  
Clinical Analyst  
Division of Cardiovascular and Renal Products /CDER

To: Dawn Williams  
DDDP

Subject: QT-IRT Consult to BLA 761067

Note: Any text in the review with a light background should be inferred as copied from the sponsor's document.

This memo responds to your consult to us dated 5/3/2017 regarding questions from the division about the potential for QT prolongation for tildrakizumab. The QT-IRT received and reviewed the following materials:

- Summary of clinical pharmacology studies (BLA 761067, Seq [0000](#));
- Highlights of Clinical Pharmacology and Cardiac Safety (Appendix 2.7.2, BLA 761067, Seq [0000](#));
- Modeling & Simulation Results Memo (BLA 761067, Seq [0000](#));
- Integrated summary of safety (BLA 761067, Seq 0000, [link](#));
- Summary of clinical safety (BLA 761067, Seq 0000, [link](#));
- Information request for BLA 761067 (dated [07/06/2017](#));
- Revised ECG outlier analysis (BLA 761067, Seq [0006](#) and Seq [0008](#));
- Meeting minutes for IND 101389 (dated [06/03/2011](#), [04/27/2012](#) and [09/20/2016](#)).

## QT-IRT Comments for DDDP

**Question 1:** Please review and comment regarding the potential of tildrakizumab to cause prolongation of the QT interval, or to otherwise adversely affect cardiac rhythm.

**QT-IRT's response:** The presented information collected across phase 1 studies suggests a low potential for QTc prolongation, consistent with tildrakizumab being a monoclonal antibody (ICH E14 Q&A (R3) 6.3). However, the ISS and clinical summary of safety includes apparently spurious RR measurements (e.g. RR of 0 ms) and QTcF at baseline in excess of 580 ms (see Appendix 2.7.4:49 in the clinical summary of safety). To resolve the issue an information request was sent to the sponsor on 07/06/2017 and the sponsor responded on 7/31/2017 stating that the spurious numbers was due to a statistical programming error that they had corrected and revised outlier tables were provided on 8/11/2017. The new tables provided supports that tildrakizumab does not prolong the QTc interval (see response to Question 2).

**Question 2:** Please also comment regarding the potential effect of tildrakizumab on any ECG changes from baseline observed during the development program.

**QT-IRT's response:** Based on analysis of the ISS data sets tildrakizumab does not appear to prolong QTc, PR or QRS.

## **BACKGROUND**

Merck Sharp & Dohme Corporation has submitted BLA 761067 for tildrakizumab, a humanized IgG1/ $\kappa$  monoclonal antibody that binds to human IL-23/P19. The proposed indication is treatment of moderate to severe plaque psoriasis in patients who are candidates for systemic therapy or phototherapy. Tildrakizumab was evaluated under IND 101389.

*Source: Consult request*

In 2011 the Division advised the sponsor to address the QT/QTc assessment early in development (DARRTs 6/3/2011). Later in 2012, the sponsor asked the Division if a thorough QT/QTc study would be required for tildrakizumab, given its molecular size. The Division agreed, but stated that the sponsor should collect periodic ECG measurements (at least baseline and at steady state). (DARRTs 4/27/2012). Lastly, at the pre-BLA meeting a comment about submission of ECG data for studies 10 and 11 was included. In the sponsor's attachment to the meeting minutes from the pre-BLA meeting, it is stated that the sponsor proposed submission only of the narratives for adjudicated events and that studies 10 and 11 included local ECG monitoring and that ECG waveforms are therefore not available (DARRTs 9/20/2016).

### **Effect of Tildrakizumab on the QT in phase 1 studies**

Antibodies are typically not associated with clinically meaningful effects on QTc interval because of their large size, which prevents interaction with the pore of hERG channels. Thus, a dedicated QTc trial was not performed for tildrakizumab; however, a highlights of clinical pharmacology table can be found in [Appendix 2.7.2: 4]. Nonetheless, a relationship between tildrakizumab concentrations and QTc was explored [Ref. 5.3.5.3: 04K8QH]. There was no evidence of QTc prolongation in an integrated analysis of the Phase 1 trials: P05382 in subjects with psoriasis; and trials P05661, P05776, and P06306 in healthy subjects. Doses were given SC (50, 200 and 400 mg) and IV (0.05, 0.1, 0.5, 3 and 10 mg/kg), with the latter giving rise to higher C<sub>max</sub> values. The analysis set was comprised of 1278 time-matched PK-electrocardiogram (ECG) observations from 192 subjects treated with tildrakizumab or placebo. Fridericia's correction (QTcF) was found to give the least correlation to ventricular rate, and was therefore used for subsequent analysis.

The number and percentage of subjects exceeding predefined values for QTcF and  $\Delta$ QTcF as defined in the ICH E14 guidance are presented in [Table 2.7.2: 17]. Thirty subjects experienced a  $\Delta$ QTcF >30 ms with a similar incidence between placebo and active treatment with (any dose of) tildrakizumab: 18.2% (6 out of 33) of the subjects in the placebo group and 15.1% (24 out of 159) of the subjects exposed to tildrakizumab experienced  $\Delta$ QTcF >30 ms.

Table 2.7.2: 17 Number and Percentage of Subjects Exceeding Predefined Values for QTcF and  $\Delta$ QTcF in the Analysis Set.

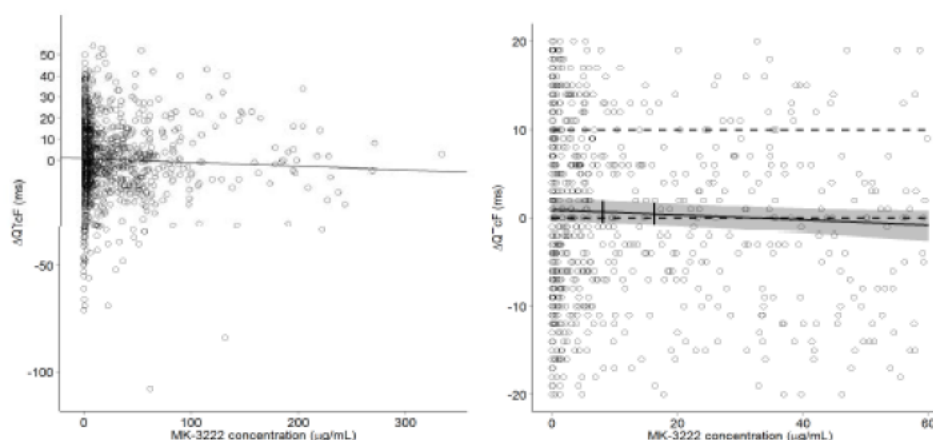
Parameter	Result % (n/N)
QTcF > 450 ms	5.7 (11/192)
QTcF > 480 ms	1.0 (2/192)
QTcF > 500 ms	0
$\Delta$ QTcF > 30 ms	15.6 (30/192)
$\Delta$ QTcF > 60 ms	0

n = number of subjects with an outlying value, N = total number of subjects,  $\Delta$ QTcF = change from baseline QTcF

Data Source: [Ref. 5.3.5.3: 04K8QH]

A linear mixed effects model identified no significant linear relationship between  $\Delta$ QTcF and tildrakizumab exposure ( $P = 0.25$ ). The effect of gender, race, route of administration (SC vs IV) and number of tildrakizumab doses (single vs multiple doses) on  $\Delta$ QTcF was tested as additional covariates in the linear models, but was found to be not statistically significant. The estimated slope suggests a (non-significant) decrease in  $\Delta$ QTcF with increasing exposure (-0.018 [95%CI]: -0.044 to 0.008) [Figure 2.7.2: 22]. Prediction intervals based on the linear mixed-effects model were derived using a bootstrap ( $n = 1000$ ).

Figure 2.7.2: 22 Scatter Plot with fitted Regression Line of  $\Delta$ QTcF vs Tildrakizumab Exposure in Healthy and Psoriatic Subjects in Phase 1 after IV and SC Administration. Left: Full Concentration Range. Right: 0 to 60  $\mu$ g/mL Concentration Range and -20 to 20 ms  $\Delta$ QTcF range



Predicted population mean (solid line) and associated bootstrap 90% CI (grey area). Dashed horizontal lines were plotted at 0 and 10 ms. Vertical lines indicate the bootstrap 90% CI of the predicted  $\Delta$ QTcF at the geometric mean C<sub>max</sub> steady-state concentration of the 100 mg SC and 200 mg SC clinical MK-3222 doses (8.1 and 16.3  $\mu$ g/mL, respectively) [Sec. 2.7.2.3.1].

Data Source: [Ref. 5.3.5.3: 04K8QH]



None of the 192 subjects included in this analysis exceeded the critical values of QTcF interval >500 ms or change from baseline in QTcF interval ( $\Delta$ QTcF) >60 ms. This analysis indicated that there was no statistically or clinically significant effect of tildrakizumab exposure on QTcF interval.

*Reviewer's Comment: Because tildrakizumab is a monoclonal antibody it is not expected to have a direct impact on the hERG potassium channel, and the clinical data described above does not suggest a potential for QTc prolongation.*

### QT assessment in phase 2b/3 studies

Change from Baseline in vital signs and ECG findings is summarized for the Phase 2b/3 Base Period Safety Pool in [Appendix 2.7.4: 49] and [Appendix 2.7.4: 50], respectively. Due to re-randomizations in different parts of the trial, these summaries were restricted to the 4 continuous exposure arms. Vital signs evaluated included diastolic blood pressure, systolic blood pressure, pulse rate, respiratory rate, and temperature. Because the 3 trials had different visit schedules, for the purpose of comparison of results across time, only the trial visits common across the Phase 2b and 3 trials are summarized. Common time points for measurement of vital signs across the Phase 2b (P05495) and Phase 3 (P010 and P011) trials during the base period were Weeks 0, 4, 8, 12, 16, 28, 40, and 52; and for the ECG parameters were Weeks 0, 4, 12, 28, and 52/64. Refer to [Table 2.7.4: 4].

Appendix 2.7.4:50 ECG findings for QTc (top) and RR (bottom)

Visit	Treatment	N	Baseline		Value		Change From Baseline	
			Mean (SD)	[Min, Max]	Mean (SD)	[Min, Max]	Mean (SD)	[Min, Max]
QTc Interval Fridericia (msec)								
Week 4	continuous exposure MK-3222 100 mg	319	404.5 (28.1)	[240.0, 584.0]	405.3 (24.0)	[349.0, 537.0]	0.8 (22.5)	[-59.0, 120.0]
	continuous exposure MK-3222 200 mg	278	408.4 (24.4)	[343.0, 572.0]	407.9 (22.6)	[356.0, 502.0]	-0.5 (21.4)	[-122.0, 87.0]
	continuous exposure MK-3222 100 / 200 mg	727	406.4 (26.1)	[240.0, 584.0]	406.2 (23.8)	[307.0, 537.0]	-0.2 (21.8)	[-122.0, 120.0]
Week 12	continuous exposure MK-3222 100 mg	317	404.4 (28.1)	[240.0, 584.0]	406.5 (22.6)	[333.0, 507.0]	2.2 (23.1)	[-105.0, 167.0]
	continuous exposure MK-3222 200 mg	276	408.5 (24.3)	[343.0, 572.0]	408.0 (29.3)	[162.0, 551.0]	-0.5 (24.6)	[-201.0, 109.0]
	continuous exposure MK-3222 100 / 200 mg	726	406.4 (26.0)	[240.0, 584.0]	407.2 (25.5)	[162.0, 551.0]	0.9 (22.7)	[-201.0, 167.0]
Week 28	continuous exposure MK-3222 100 mg	317	404.3 (28.1)	[240.0, 584.0]	404.9 (23.9)	[301.0, 525.0]	0.6 (23.7)	[-152.0, 125.0]
	continuous exposure MK-3222 200 mg	276	408.3 (24.4)	[343.0, 572.0]	408.2 (25.3)	[315.0, 553.0]	-0.0 (22.2)	[-119.0, 171.0]
	continuous exposure MK-3222 100 / 200 mg	724	406.2 (26.0)	[240.0, 584.0]	406.4 (24.9)	[301.0, 553.0]	0.2 (22.4)	[-152.0, 171.0]
Week 52/64	continuous exposure MK-3222 100 mg	314	404.4 (28.2)	[240.0, 584.0]	405.0 (22.9)	[318.0, 492.0]	0.6 (25.3)	[-115.0, 131.0]
	continuous exposure MK-3222 200 mg	276	408.3 (24.3)	[343.0, 572.0]	407.3 (22.8)	[337.0, 498.0]	-1.0 (21.3)	[-155.0, 99.0]
	continuous exposure MK-3222 100 / 200 mg	724	406.3 (26.0)	[240.0, 584.0]	406.4 (23.3)	[318.0, 506.0]	0.2 (23.6)	[-155.0, 131.0]

Visit	Treatment	N	Baseline		Value		Change From Baseline	
			Mean (SD)	[Min, Max]	Mean (SD)	[Min, Max]	Mean (SD)	[Min, Max]
RR Interval (msec)								
Week 4	continuous exposure MK-3222 100 mg	318	347.5 (387.6)	[60.0, 1398.0]	338.9 (376.4)	[60.0, 1352.0]	-8.6 (63.6)	[-358.0, 207.0]
	continuous exposure MK-3222 200 mg	276	436.3 (413.7)	[40.0, 1340.0]	431.5 (409.6)	[40.0, 1289.0]	-4.8 (80.0)	[-314.0, 332.0]
	continuous exposure MK-3222 100 / 200 mg	726	349.1 (385.7)	[0.0, 1398.0]	343.8 (378.7)	[40.0, 1352.0]	-5.3 (66.5)	[-358.0, 332.0]
Week 12	continuous exposure MK-3222 100 mg	317	344.5 (384.7)	[60.0, 1398.0]	340.3 (378.2)	[40.0, 1250.0]	-4.2 (55.6)	[-244.0, 233.0]
	continuous exposure MK-3222 200 mg	274	427.4 (409.1)	[40.0, 1340.0]	433.3 (414.9)	[40.0, 1263.0]	5.9 (77.3)	[-304.0, 420.0]
	continuous exposure MK-3222 100 / 200 mg	724	344.0 (381.5)	[0.0, 1398.0]	345.3 (382.5)	[40.0, 1263.0]	1.3 (62.1)	[-304.0, 420.0]
Week 28	continuous exposure MK-3222 100 mg	316	342.7 (384.2)	[60.0, 1398.0]	338.5 (379.6)	[48.0, 1269.0]	-4.2 (70.1)	[-338.0, 338.0]
	continuous exposure MK-3222 200 mg	273	428.5 (409.4)	[40.0, 1340.0]	431.0 (411.6)	[40.0, 1240.0]	2.4 (75.3)	[-360.0, 317.0]
	continuous exposure MK-3222 100 / 200 mg	720	342.8 (381.2)	[0.0, 1398.0]	343.3 (382.0)	[40.0, 1274.0]	0.5 (68.7)	[-360.0, 370.0]
Week 52/64	continuous exposure MK-3222 100 mg	315	338.5 (382.5)	[60.0, 1398.0]	342.2 (390.2)	[48.0, 1334.0]	3.7 (70.2)	[-331.0, 292.0]
	continuous exposure MK-3222 200 mg	274	427.5 (409.0)	[40.0, 1340.0]	439.4 (421.0)	[55.0, 1200.0]	12.0 (72.9)	[-297.0, 360.0]
	continuous exposure MK-3222 100 / 200 mg	723	339.6 (379.8)	[0.0, 1398.0]	346.3 (389.7)	[48.0, 1334.0]	6.7 (65.8)	[-331.0, 360.0]

*Reviewer's Comment: The tables shown above appear to be erroneous as they include RR measurements of 0 ms and an overall mean of 300 to 400 ms (which corresponds to 150 to 200 bpm). The data sets used for the tables above were not provided, but an ISS data set containing*

ECG data from studies P010 and P011 was provided as well as summary tables for that data alone (which has similarly spurious numbers). To resolve this issue an information request (DARRTs 07/06/2017) was sent to the company and the company clarified that a mistake was made in the original tables (Seq 0006) and revised tables were provided, which are included below and does not suggest a potential for QTc prolongation (Seq 0008).

**Table 1: ECG outlier table for phase 2 and 3 studies.**  
*[Source: Revised ECG outlier analysis, Seq 0008, Table 1]*

Criterion	Placebo N=355 n/m (%)	MK-3222 100mg N=705 n/m (%)	MK-3222 200mg N=708 n/m (%)	MK-3222 100 / 200mg N=1413 n/m (%)	Elanrecept 50mg N=313 n/m (%)
<b>QTc Interval Bazett (msec)</b>					
QTcB > 500	1 / 252 (0.40)	0 / 476 (0.00)	5 / 484 (1.03)	5 / 960 (0.52)	0 / 256 (0.00)
QTcB > 480	4 / 250 (1.60)	8 / 474 (1.69)	9 / 476 (1.89)	17 / 950 (1.79)	3 / 255 (1.18)
QTcB > 450	20 / 233 (8.58)	32 / 446 (7.17)	32 / 447 (7.16)	64 / 893 (7.17)	15 / 243 (6.17)
QTcB changes from baseline > 30	33 / 254 (12.99)	47 / 480 (9.79)	43 / 488 (8.81)	90 / 968 (9.30)	24 / 257 (9.34)
QTcB changes from baseline > 60	6 / 254 (2.36)	5 / 480 (1.04)	3 / 488 (0.61)	8 / 968 (0.83)	6 / 257 (2.33)
<b>QTc Interval Fridericia (msec)</b>					
QTcF > 500	1 / 254 (0.39)	1 / 476 (0.21)	1 / 487 (0.21)	2 / 963 (0.21)	0 / 256 (0.00)
QTcF > 480	1 / 253 (0.40)	2 / 475 (0.42)	2 / 486 (0.41)	4 / 961 (0.42)	0 / 256 (0.00)
QTcF > 450	6 / 245 (2.45)	10 / 471 (2.12)	14 / 467 (3.00)	24 / 938 (2.56)	8 / 253 (3.16)
QTcF changes from baseline > 30	17 / 254 (6.69)	27 / 480 (5.63)	21 / 488 (4.30)	48 / 968 (4.96)	19 / 257 (7.39)
QTcF changes from baseline > 60	6 / 254 (2.36)	3 / 480 (0.63)	3 / 488 (0.61)	6 / 968 (0.62)	3 / 257 (1.17)
<b>PR Interval (msec)</b>					
PR > 200	10 / 283 (3.53)	19 / 566 (3.36)	23 / 577 (3.99)	42 / 1143 (3.67)	11 / 282 (3.90)
PR > 220	5 / 297 (1.68)	6 / 584 (1.03)	7 / 599 (1.17)	13 / 1183 (1.10)	7 / 296 (2.36)
PR > 240	3 / 299 (1.00)	2 / 588 (0.34)	3 / 600 (0.50)	5 / 1188 (0.42)	2 / 297 (0.67)
<b>QRS Interval (msec)</b>					
QRS > 110	20 / 282 (7.09)	29 / 564 (5.14)	39 / 565 (6.90)	68 / 1129 (6.02)	15 / 276 (5.43)
N=number of subjects in each treatment arm. n=number of subjects with most extreme value meeting the criterion post-baseline (new or worsened compared to baseline). m=number of subjects with baseline and at least one post-baseline data who are not meeting the criterion at baseline.					

Source: [ISS: analysis-ads]; adeg]

Thank you for requesting our input into the development of this product under BLA 761067. We welcome more discussion with you now and in the future. Please feel free to contact us via email at [cdcrdcrpqt@fda.hhs.gov](mailto:cdcrdcrpqt@fda.hhs.gov)

**Table 2: Highlights of Clinical Pharmacology and Cardiac Safety**

Therapeutic dose	Subjects with moderate to severe psoriasis should receive a regimen of 100 mg SC (one 100 mg injection) at Week 0, Week 4 and every 12 weeks thereafter (Q12W). Subjects with psoriasis with body weight > 90 kg may benefit from a dose of 200 mg SC (two 100 mg injections).	
Maximum tolerated dose	Not evaluated.	
Principal adverse events	diarrhoea; bronchitis; nasopharyngitis; sinusitis; upper respiratory tract infection; arthralgia; back pain; headache; cough; hypertension.	
Maximum dose tested	Single Dose	10 mg/kg IV in healthy subjects
	Multiple Dose	10 mg/kg IV on Day 1, Day 28 and Day 56 in subjects with psoriasis
Exposures Achieved at Maximum Tested Dose	Single Dose	AUC <sub>0-∞</sub> AM (CV%): 4560 (5%) µg/mL·day C <sub>max</sub> AM (CV%): 261 (8%) µg/mL·day
	Multiple Dose	AUC (Day28-Day56) AM (%CV): 3670 (20%) µg/mL·day AUC <sub>0-∞</sub> (3 <sup>rd</sup> Dose) <sup>†</sup> AM (CV%): 6360 (NC) µg/mL·day C <sub>max</sub> (3 <sup>rd</sup> Dose) AM (CV%): 297 (22%) µg/mL
Range of linear PK	Over the dose range of 50 mg to 400 mg SC, which includes the clinically relevant doses of 100 and 200 mg, tildrakizumab exposure increased proportionally with dose	
Accumulation	Steady-state is achieved by 16 weeks with the clinical regimen (dosing on Week 0 and Week 4 and Q12W thereafter) with 1.1-fold accumulation in C <sub>max</sub> .	
Metabolites	As tildrakizumab is a monoclonal antibody, there are no active metabolites.	
Absorption	Absolute/Relative Bioavailability	No formal absolute bioavailability has been performed in humans. An explorative evaluation of 50 and 200 mg SC in P05776 relative to 0.5 mg/kg and 3 mg/kg IV P05661 (individual body weight corrected) indicated an absolute bioavailability of 80% and 73%, respectively. Another explorative evaluation of dose-normalized 400 mg SC and 10 mg/kg IV in Japanese subjects in P06306 found an absolute bioavailability of 92%.  A POP PK model found that the lyophilized SC formulation in early development had a 5% lower relative bioavailability compared to the lyophilized SC formulation housed in a PFS (commercial image), which is within the clinical comparability bounds.
	T <sub>max</sub>	GM (CV%) 6.2 days (46%)
Distribution	V <sub>dss</sub> /F	GM (CV%) 10.8 L (24%)
	% bound	No traditional plasma protein binding studies have been performed. Tildrakizumab is not expected to bind to plasma proteins
Elimination	Route	Tildrakizumab is catabolized into component amino acids by general protein degradation processes and is not eliminated by renal or hepatic pathways. Apparent clearance is independent of dose.
	Terminal t <sub>½</sub>	GM (%CV) Apparent elimination half-life is 23.4 days (23%)
	CL/F	GM (%CV) apparent clearance of 0.32 L/day (38%)
Intrinsic Factors	Age	A dedicated trial to evaluate the effect age on PK was not conducted.

		<p>The POP PK model was used to simulate tildrakizumab PK in non-elderly (&lt; 65 yrs) and elderly (≥ 65 yrs) subjects using distributions of other covariates derived from the psoriasis subjects enrolled in the Phase 2b and 3 trials. The resulting steady-state AUC GMRs [90% CI] for non-elderly (&lt; 65 yrs)/elderly (≥ 65 yrs) subjects receiving 100 mg and 200 mg SC were 0.89 [0.83-0.95] and 0.91 [0.85-0.98], respectively.</p>
	Sex	<p>A dedicated trial to evaluate the effect of gender on tildrakizumab PK was not conducted. The POP PK model was used to simulate tildrakizumab PK in males and females using distributions of other covariates derived from the psoriasis subjects enrolled in the Phase 2b and 3 trials. The resulting steady-state AUC GMRs [90% CI] for females/males receiving 100 mg and 200 mg SC were 1.01 [0.97-1.06] and 1.01 [0.96-1.05], respectively.</p>
	Race	<p>A POP PK model was used to simulate tildrakizumab PK in Asian vs white and Other (including black) subjects using distributions of other covariates derived from the psoriasis subjects enrolled in the Phase 2b and 3 trials. The resulting AUCSS GMRs [90% CI] for Asian/white and Other (including black)/white psoriatic subjects receiving 100 mg SC were 1.06 [1.00-1.12] and 0.85 [0.78-0.92], respectively and for 200 mg SC 1.04 [0.98-1.10] and 0.82 [0.82-0.99], respectively. These effects are well within the clinical significance bounds for tildrakizumab.</p> <p>In addition, results from an ethnic sensitivity (Japanese compared to white subjects) trial indicate the geometric mean ratios (white/Japanese) and 90% CIs were 1.03 (0.94, 1.12) and 0.93 (0.83, 1.05) for AUC<sub>0-∞</sub> and C<sub>max</sub>, respectively.</p>
	Hepatic & Renal Impairment	<p>Dedicated hepatic and renal trials were not conducted to assess the effect of organ impairment on tildrakizumab PK (see elimination). The POP PK model was used to simulate tildrakizumab PK in subjects with normal CRCL (≥ 50 mL/min) and subjects with decreased CRCL (&lt; 50 mL/min) using distributions of other covariates derived from the psoriasis subjects enrolled in the Phase 2b and 3 trials. The resulting steady-state AUC GMRs [90% CI] for normal CRCL (≥ 50 mL/min)/decreased CRCL (&lt; 50 mL/min) subjects receiving 100 mg and 200 mg SC were 1.01 [0.78-1.32] and 1.00 [0.73-1.35], respectively.</p>
Extrinsic Factors	Drug interactions	<p>No dedicated DDI trials were conducted. Biologics, such as tildrakizumab, do not undergo typical metabolism or use transporter pathways which are relevant to small molecules. The lack of overlapping pathways is expected to limit the potential for PK based interactions. Therefore, concomitant small molecule medications are not anticipated to affect the PK of tildrakizumab.</p> <p>A POP PK model was used to simulate tildrakizumab PK in subjects with and without use of corticosteroids and with and without prior use of biologic therapy. The resulting AUCSS GMRs [90% CI] for subjects with/without concomitant systemic corticosteroids receiving 100 mg and 200 mg SC were 0.96 [0.80-1.14] and 1.02 [0.82-1.26], respectively. The resulting AUCSS GMRs [90% CI] for subjects with/without prior treatment of psoriasis with a biological agent receiving 100 mg and 200 mg SC were 0.90 [0.85-0.95] and 0.89 [0.85-0.84], respectively.</p>

	Food Effects	Not applicable as tildrakizumab is administered SC.
Expected High Clinical Exposure Scenario	No intrinsic nor extrinsic factor resulted in a greater than 50% increase in tildrakizumab exposure. The highest projected clinical dose is 200 mg. Steady-state treatment with 200 mg SC tildrakizumab in psoriatic subjects results in geometric means (%CV) of AUC0-Week12 and Cmax of 612 µg•day/mL (40%) and 16.3 µg/mL (33%), respectively. Therefore the high clinical exposure scenario is covered by the AUC and Cmax values observed with the 10 mg/kg IV dose.	
† AUC0-∞ (3 <sup>rd</sup> Dose) is calculated from Part 2 of P05382: 10 mg/kg IV AUC0-∞ (Day1 to infinity) minus partial AUC (Day1-28) and minus partial AUC (Day28-56).		
SC = subcutaneous, POP PK = population pharmacokinetic, AM = Arithmetic Mean, GM =Geometric mean.		

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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.**  
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/s/  
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LARS JOHANNESSEN  
09/29/2017

CHRISTINE E GARNETT  
09/29/2017



## **DEPARTMENT OF HEALTH & HUMAN SERVICES**

**Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of New Drugs  
Division of Pulmonary, Allergy and Rheumatology Products (DPARP)  
10903 New Hampshire Avenue, Silver Spring, MD 20993**

### **Consultative Review for DDDP**

**Date:** September 21, 2017

**From:** Stefanie Freeman, M.D.  
Clinical Reviewer, DPARP

**To:** Kevin Clark, M.D.  
Clinical Reviewer, DDDP

Melinda McCord, M.D.  
Clinical Reviewer, DDDP

**Through:** Nikolay P. Nikolov, M.D.  
Clinical Team Leader, DPARP

Badrul Chowdhury, M.D., Ph.D.  
Division Director, DPARP

**Product:** Tildrakizumab

**Indication:** Moderate to Severe Plaque Psoriasis in patients who are candidates for systemic therapy or phototherapy

**Sponsor:** Merck Sharp & Dohme Corporation

**Re:** BLA # 761067 (IND # 101389) regarding the sufficiency of evaluation of (b) (4) in the submitted BLA to support labeling claims or future promotional language.

20 Page(s) has been Withheld in Full as b4 (CCI/TS)  
immediately following this page

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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.**  
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/s/  
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STEFANIE H FREEMAN  
09/25/2017

NIKOLAY P NIKOLOV  
09/25/2017  
I concur.

BADRUL A CHOWDHURY  
09/26/2017



## 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# 761067	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"/> Labeling Change With Clinical Data (SE8) <input type="checkbox"/> Manufacturing Change With Clinical Data (SE9) <input type="checkbox"/> Animal Rule Confirmatory Study (SE10)
Proprietary Name: Established/Proper Name: tildrakizumab Dosage Form: injectable Strengths: 100 mg/mL Route(s) of Administration: subcutaneous		
Applicant: Merck Sharp & Dohme Corp Agent for Applicant (if applicable):		
Date of Application: March 23, 2017 Date of Receipt: March 23, 2017 Date clock started after Unacceptable for Filing (UN):		
PDUFA/BsUFA Goal Date: March 23, 2018		Action Goal Date (if different):
Filing Date: May 22, 2017		Date of Filing Meeting: May 11, 2017
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 <input type="checkbox"/> Type 9-New Indication or Claim (will <u>not</u> be marketed as a separate NDA after approval) <input type="checkbox"/> Type 10-New Indication or Claim (will be marketed as a separate NDA after approval)		
Proposed indication(s)/Proposed change(s):		
Type of Original NDA: AND (if applicable) Type of NDA Supplement:  <i>If 505(b)(2)NDA/NDA Supplement: Draft the “505(b)(2) Assessment” review found at:</i> <a href="http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027499">http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027499</a> .		<input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2) <input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2)
Type of BLA  <i>If 351(k), notify the OND Therapeutic Biologics and Biosimilars Team</i>		<input checked="" type="checkbox"/> 351(a) <input type="checkbox"/> 351(k)

Review Classification:  <i>The application will be a priority review if:</i> <ul style="list-style-type: none"> <li>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)</li> <li>The product is a Qualified Infectious Disease Product (QIDP)</li> <li>A Tropical Disease Priority Review Voucher was submitted</li> <li>A Pediatric Rare Disease Priority Review Voucher was submitted</li> </ul>		<input checked="" type="checkbox"/> Standard <input type="checkbox"/> Priority  <input type="checkbox"/> Pediatric WR <input type="checkbox"/> QIDP <input type="checkbox"/> Tropical Disease Priority Review Voucher <input type="checkbox"/> Pediatric Rare Disease Priority Review Voucher		
Resubmission after withdrawal? <input type="checkbox"/>		Resubmission after refuse to file? <input type="checkbox"/>		
Part 3 Combination Product? <input type="checkbox"/>  <i>If yes, contact the Office of Combination Products (OCP) and copy them on all Inter-Center consults</i>		<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)		
<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: <ul style="list-style-type: none"> <li><input type="checkbox"/> FDAAA [505(o)]</li> <li><input type="checkbox"/> PREA deferred pediatric studies (FDCA Section 505B)</li> <li><input type="checkbox"/> Accelerated approval confirmatory studies (21 CFR 314.510/21 CFR 601.41)</li> <li><input type="checkbox"/> Animal rule postmarketing studies to verify clinical benefit and safety (21 CFR 314.610/21 CFR 601.42)</li> </ul>		
Collaborative Review Division (if OTC product):				
List referenced IND Number(s): IND 101389				
Goal Dates/Product Names/Classification Properties	YES	NO	NA	Comment
PDUFA/BsUFA and Action Goal dates correct in the electronic archive?  <i>If no, ask the document room staff to correct them immediately. These are the dates used for calculating inspection dates.</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
Are the established/proper and applicant names correct in electronic archive?  <i>If no, ask the document room staff to make the corrections. Also, ask the document room staff to add the established/proper name to the supporting IND(s) if not already entered into electronic archive.</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>		

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> <a href="http://inside.fda.gov:9003/CDER/OfficeofBusinessProcessSupport/ucm163969.htm">http://inside.fda.gov:9003/CDER/OfficeofBusinessProcessSupport/ucm163969.htm</a>  <i>If no, ask the document room staff to make the appropriate entries.</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<b>Application Integrity Policy</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is the application affected by the Application Integrity Policy (AIP)? <i>Check the AIP list at:</i> <a href="http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm">http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm</a>	<input type="checkbox"/>	<input checked="" type="checkbox"/>		
If yes, explain in comment column.				
If affected by AIP, has OC been notified of the submission? If yes, date notified:	<input type="checkbox"/>	<input type="checkbox"/>		
<b>User Fees</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
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 from receipt. Review stops. Contact the User Fee Staff. If appropriate, send UN letter.</i>	Payment for this application ( <i>check daily email from <a href="mailto:UserFeeAR@fda.hhs.gov">UserFeeAR@fda.hhs.gov</a>:</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. Contact the User Fee Staff. If appropriate, send UN letter.</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> <a href="http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM079320.pdf">http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM079320.pdf</a>	Has the user fee bundling policy been appropriately applied? <i>If no, or you are not sure, consult the User Fee Staff.</i> <input checked="" type="checkbox"/> Yes <input type="checkbox"/> No			
<b>505(b)(2) (NDAs/NDA Efficacy Supplements only)</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is the application a 505(b)(2) NDA? ( <i>Check the 356h form, cover letter, and annotated labeling</i> ). <b>If yes</b> , answer the bulleted questions below:	<input type="checkbox"/>	<input type="checkbox"/>		
<ul style="list-style-type: none"> <li>Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?</li> </ul>	<input type="checkbox"/>	<input type="checkbox"/>		

<ul style="list-style-type: none"> <li>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)].</li> </ul>	<input type="checkbox"/>	<input type="checkbox"/>																		
<ul style="list-style-type: none"> <li>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)]?</li> </ul> <p><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></p>	<input type="checkbox"/>	<input type="checkbox"/>																		
<ul style="list-style-type: none"> <li>Is there unexpired exclusivity on another listed drug product containing the same active moiety (e.g., 5-year, 3-year, orphan, or pediatric exclusivity)?</li> </ul> <p><b>Check the Electronic Orange Book at:</b>  <a href="http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm">http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm</a></p> <p><b>If yes, please list below:</b></p> <table border="1"> <thead> <tr> <th>Application No.</th> <th>Drug Name</th> <th>Exclusivity Code</th> <th>Exclusivity Expiration</th> </tr> </thead> <tbody> <tr><td> </td><td> </td><td> </td><td> </td></tr> <tr><td> </td><td> </td><td> </td><td> </td></tr> <tr><td> </td><td> </td><td> </td><td> </td></tr> </tbody> </table>	Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration													<input type="checkbox"/>	<input type="checkbox"/>		
Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration																	
<p><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 and GAIN exclusivity will extend both of the timeframes in this provision by 6 months and five years, respectively. 21 CFR 314.108(b)(2). Unexpired orphan or 3-year exclusivity may block the approval but not the submission of a 505(b)(2) application.</i></p>																				
<ul style="list-style-type: none"> <li>If FDA has approved one or more pharmaceutically equivalent (PE) products in one or more NDAs before the submission date of the original 505(b)(2) application, did the applicant identify one such product as a listed drug (or an additional listed drug) relied upon and provide an appropriate patent certification or statement [see 21 CFR 314.50(i)(1)(i)(C) and 314.54]?</li> </ul> <p><b>Check the Electronic Orange Book at:</b>  <a href="http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm">http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm</a></p> <p><b>If no, include template language in the 74-day letter.</b></p> <p><b>Failure to identify a PE is an approvability issue but not a filing issue [see 21 CFR 314.125(b)(19)]</b></p> <p><b>Note: Pharmaceutical equivalents</b> are drug products in identical dosage forms and route(s) of administration that: <b>(1)</b> contain identical amounts of the identical active drug ingredient, i.e., the same salt or ester of the same therapeutic moiety, or, in the case of modified release dosage forms that require a reservoir or overage or such forms as prefilled syringes where residual volume may vary, that deliver identical amounts of the active drug ingredient over the identical dosing period; <b>(2)</b> do not necessarily contain the same inactive ingredients; <b>and (3)</b> meet the identical compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times, and/or dissolution rates.</p>	<input type="checkbox"/>	<input type="checkbox"/>																		

Exclusivity	YES	NO	NA	Comment
Does another product (same active moiety) have orphan exclusivity for the same indication? <b>Check the Orphan Drug Designations and Approvals list at:</b> <a href="http://www.accessdata.fda.gov/scripts/opdlisting/oopd/index.cfm">http://www.accessdata.fda.gov/scripts/opdlisting/oopd/index.cfm</a>	<input type="checkbox"/>	<input type="checkbox"/>		
<b>If another product has orphan exclusivity</b> , is the product considered to be the same product according to the orphan drug definition of sameness [see 21 CFR 316.3(b)(14)]?  <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"/>	
<b>NDAs/NDA efficacy supplements only:</b> Has the applicant requested 5-year or 3-year Waxman-Hatch exclusivity?  <b>If yes, # years requested:</b>  <i>Note: An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<b>NDAs only:</b> 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"/>	
<b>If yes</b> , 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"/>	
<b>BLAs only:</b> Has the applicant requested 12-year exclusivity under section 351(k)(7) of the PHS Act?  <i>If yes, notify Marlene Schultz-DePalo, CDER Purple Book Manager</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				
<p><i>Do not check mixed submission if the only electronic component is the content of labeling (COL).</i></p>	<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)			
<p><b>If mixed (paper/electronic) submission</b>, which parts of the application are submitted in electronic format?</p>				
<b>Overall Format/Content</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
<p><b>If electronic submission</b>, does it follow the eCTD guidance?<sup>1</sup>  <b>If not</b>, explain (e.g., waiver granted).</p>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<p><b>Index:</b> Does the submission contain an accurate comprehensive index?</p>	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
<p>Is the submission complete as required under 21 CFR 314.50 (<i>NDA</i>s/<i>NDA</i> efficacy supplements) or under 21 CFR 601.2 (<i>BLA</i>s/<i>BLA</i> efficacy supplements) including:</p> <p><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)</p> <p><b>If no</b>, explain.</p>	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
<p><b>BLAs only:</b> Companion application received if a shared or divided manufacturing arrangement?</p> <p><b>If yes</b>, BLA #</p>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	Not a companion application
<b>Forms and Certifications</b>				
<p><i>Electronic forms and certifications with electronic signatures (scanned, digital, or electronic – similar to DARRTS, e.g., /s/) are acceptable. Otherwise, <b>paper</b> forms and certifications with hand-written signatures must be included.</i></p> <p><b>Forms</b> include: user fee cover sheet (3397/3792), application form (356h), patent information (3542a), financial disclosure (3454/3455), and clinical trials (3674); <b>Certifications</b> include: debarment certification, patent certification(s), field copy certification, and pediatric certification.</p>				
<b>Application Form</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
<p>Is form FDA 356h included with authorized signature per 21 CFR 314.50(a)?</p> <p><i>If foreign applicant, a U.S. agent must sign the form [see 21 CFR 314.50(a)(5)].</i></p>	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
<p>Are all establishments and their registration numbers listed on the form/attached to the form?</p>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	

<sup>1</sup> <http://www.fda.gov/ucm/groups/fdagov-public/@fdagov-drugs-gen/documents/document/ucm333969.pdf>

<b>Patent Information (NDAs/NDA efficacy supplements only)</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is patent information submitted on form FDA 3542a per 21 CFR 314.53(c)?	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
<b>Financial Disclosure</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Are financial disclosure forms FDA 3454 and/or 3455 included with authorized signature per 21 CFR 54.4(a)(1) and (3)?  <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>	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
<b>Clinical Trials Database</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is form FDA 3674 included with authorized signature?  <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>	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
<b>Debarment Certification</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
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&amp;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"/>	
<b>Field Copy Certification (NDAs/NDA efficacy supplements only)</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
<b>For paper submissions only:</b> 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 checked="" type="checkbox"/>	

Controlled Substance/Product with Abuse Potential	YES	NO	NA	Comment
<p>For NMEs: Is an Abuse Liability Assessment, including a proposal for scheduling, submitted per 21 CFR 314.50(d)(5)(vii)?</p> <p><i>If yes, date consult sent to the Controlled Substance Staff:</i></p> <p>For non-NMEs: <i>Date of consult sent to Controlled Substance Staff:</i></p>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
Pediatrics	YES	NO	NA	Comment
<p><b><u>PREA</u></b></p> <p>Does the application trigger PREA?</p> <p><i>If yes, notify <a href="mailto:PeRC@fda.hhs.gov">PeRC@fda.hhs.gov</a> to schedule required PeRC meeting<sup>2</sup></i></p> <p><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 &amp; deferral requests, pediatric plans, and pediatric assessment studies must be reviewed by PeRC prior to approval of the application/supplement.</i></p>	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
<p><b>If the application triggers PREA</b>, is there an agreed Initial Pediatric Study Plan (iPSP)?</p> <p><i>If no, may be an RTF issue - contact DPMH for advice.</i></p>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<p><b>If required by the agreed iPSP</b>, are the pediatric studies outlined in the agreed iPSP completed and included in the application?</p> <p><i>If no, may be an RTF issue - contact DPMH for advice.</i></p>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
<p><b><u>BPCA:</u></b></p> <p>Is this submission a complete response to a pediatric Written Request?</p> <p><i>If yes, notify Pediatric Exclusivity Board RPM (pediatric exclusivity determination is required<sup>3</sup></i></p>	<input type="checkbox"/>	<input checked="" type="checkbox"/>		

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<http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/OfficeofNonprescriptionProducts/PediatricandMaternalHealthStaff/ucm027829.htm>

3

<http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/OfficeofNonprescriptionProducts/PediatricandMaternalHealthStaff/ucm027837.htm>

Version: 12/05/2016

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Proprietary Name	YES	NO	NA	Comment
Is a proposed proprietary name submitted?  <i>If yes, ensure that the application is also coded with the supporting document category, "Proprietary Name/Request for Review."</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	Submitted April 10, 2017
REMS	YES	NO	NA	Comment
Is a REMS submitted?  <i>If yes, send consult to OSE/DRISK and notify OC/ OSI/DSC/PMSB via the CDER OSI RMP mailbox</i>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	
Prescription Labeling	<input type="checkbox"/> Not applicable			
Check all types of labeling submitted.	<input checked="" type="checkbox"/> Package Insert (Prescribing Information)(PI) <input type="checkbox"/> Patient Package Insert (PPI) <input type="checkbox"/> Instructions for Use (IFU) <input type="checkbox"/> Medication Guide (MedGuide) <input checked="" type="checkbox"/> Carton labeling <input checked="" type="checkbox"/> Immediate container labels <input type="checkbox"/> Diluent labeling <input type="checkbox"/> Other (specify)			
	YES	NO	NA	Comment
Is Electronic Content of Labeling (COL) submitted in SPL format?  <i>If no, request applicant to submit SPL before the filing date.</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
Is the PI submitted in Physician Labeling Rule (PLR) format? <sup>4</sup>	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
<b>If PI not submitted in PLR format</b> , was a waiver or deferral requested before the application was received or in the submission? <b>If requested before application was submitted</b> , 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"/>	
<b>For applications submitted on or after June 30, 2015:</b> Is the PI submitted in Pregnancy and Lactation Labeling Rule (PLLR) format?  Has a review of the available pregnancy, lactation, and females and males of reproductive potential data (if applicable) been included?	<input checked="" type="checkbox"/>          <input checked="" type="checkbox"/>	<input type="checkbox"/>          <input type="checkbox"/>	<input type="checkbox"/>          <input type="checkbox"/>	
<b>For applications submitted on or after June 30, 2015:</b> <b>If PI not submitted in PLLR format</b> , was a waiver or deferral requested before the application was received or in the submission? <b>If requested before application was submitted</b> , what is the status of the request?  <i>If no waiver or deferral, request applicant to submit labeling in PLLR format before the filing date.</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	

<sup>4</sup> <http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/LabelingDevelopmentTeam/ucm025576.htm>

Has all labeling [(PI, patient labeling (PPI, MedGuide, IFU), carton and immediate container labeling)] been consulted to OPDP?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Has PI and patient labeling (PPI, MedGuide, IFU) been consulted to OSE/DRISK? ( <i>send WORD version if available</i> )	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
Has all labeling [PI, patient labeling (PPI, MedGuide, IFU) carton and immediate container labeling, PI, PPI been consulted/sent to OSE/DMEPA and appropriate CMC review office in OPQ (OBP or ONDP)?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<b>OTC Labeling</b>	<input checked="" type="checkbox"/> <b>Not Applicable</b>			
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 (specify)			
	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is electronic content of labeling (COL) submitted?	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
<i>If no, request in 74-day letter.</i>				
Are annotated specifications submitted for all stock keeping units (SKUs)?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<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"/>	
<b>Other Consults</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
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"/>	The following consults have been finalized: ICC (CDRH); DMEPA; Human Factors; DCRP; DPMH; DPP; QT/IRT; OSI
<i>If yes, specify consult(s) and date(s) sent:</i>				
<b>Meeting Minutes/SPAs</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
End-of Phase 2 meeting(s)? <b>Date(s):</b> April 11, 2012	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
Pre-NDA/Pre-BLA/Pre-Supplement meeting(s)? <b>Date(s):</b> August 31, 2016	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
Any Special Protocol Assessments (SPAs)?	<input checked="" type="checkbox"/>			

**Date(s):** July 18, 2012 (3)

# ATTACHMENT

## MEMO OF FILING MEETING

**DATE:** May 11, 2017

**BACKGROUND:** The applicant is seeking an indication for the treatment of moderate to severe plaque psoriasis.

**Meetings:** August 31, 2016 Pre-BLA Meeting; July 29, 2013 Guidance Meeting; April 11, 2012 End of Phase 2 Meeting; March 21, 2012 Exec CAC; June 1, 2011 Guidance Meeting

**Correspondences:** June 9, 2016 Agreed iPSP; March 8, 2016 Advice (on pre-filled syringe); July 18, 2012 SPA (3)

### REVIEW TEAM:

Discipline/Organization	Names		Present at filing meeting? (Y or N)
Regulatory Project Management	RPM:	Williams	Y
	CPMS/TL:	Gould	Y
Cross-Discipline Team Leader (CDTL)	Diglisic		Y
Division Director/Deputy	Lindstrom		Y
Office Director/Deputy	Beitz		Y
	Marcus		Y
Clinical	Reviewer:	Clark McCord	Y Y
	TL:	Diglisic	Y
Clinical Pharmacology	Reviewer:	J. Wang	Y
	TL:	Y. Wang	Y
• Genomics	Reviewer:		
• Pharmacometrics	Reviewer:		
Biostatistics	Reviewer:	Guerra	Y
	TL:	Alosh	Y

Nonclinical Pharmacology/Toxicology)	Reviewer:	Wang	Y
	TL:	Hill	Y
Statistics (carcinogenicity)	Reviewer:		
	TL:		
Product Quality (CMC) Review Team:	ATL:	Hallett	Y
	RBPM:		
• OBP Drug Substance	Reviewer:	Wadkins	Y
• OBP Drug Product	Reviewer:	Shukla	Y
• OPF Reviewer	Reviewer:	T. Nguyen	Y
• DMA DS Reviewer	Reviewer:	B. Chi	Y
• DMA DP Reviewer	Reviewer:	M. Crawford	Y
• DMA Qual	Reviewer:	Palmer	Y
• Other (e.g., Branch Chiefs, EA Reviewer)			
OMP/OMPI/DMPP (MedGuide, PPI, IFU)	Reviewer:		
	TL:		
OMP/OPDP (PI, PPI, MedGuide, IFU, carton and immediate container labeling)	Reviewer:		
	TL:		
OSE/DMEPA (proprietary name, carton/container labeling)	Reviewer:	Carlos Mena-Grillasca	Y
	TL:	Mishale Mistry	N
OSE/DRISK (REMS)	Reviewer:	Weintraub	Y
	TL:	Chan	Y
OC/OSI/DSC/PMSB (REMS)	Reviewer:		
	TL:		

Bioresearch Monitoring (OSI)	Reviewer:		
	TL:		
Controlled Substance Staff (CSS)	Reviewer:		
	TL:		
Other reviewers/disciplines			
<ul style="list-style-type: none"> <li><b>Discipline</b></li> </ul> <p><small>*For additional lines, highlight this group of cells, copy, then paste: select "insert as new rows"</small></p>	Reviewer:		
	TL:		
Other attendees	K. Marin (CDRH		Y
	T. Bui Nguen OSE RPM		Y
	N. Xu DDDP ADL		Y
	<small>*For additional lines, right click here and select "insert rows below"</small>		

### **FILING MEETING DISCUSSION:**

<b>GENERAL</b>	
<ul style="list-style-type: none"> <li>505(b)(2) filing issues: <ul style="list-style-type: none"> <li>Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?</li> <li>Did the applicant provide a scientific "bridge" demonstrating the relationship between the proposed product and the referenced product(s)/published literature?</li> </ul> <p>Describe the scientific bridge (e.g., information to demonstrate sufficient similarity between the proposed product and the listed drug(s) such as BA/BE studies or to justify reliance on information described in published literature):</p> </li> </ul>	<input checked="" type="checkbox"/> Not Applicable  <input type="checkbox"/> YES <input type="checkbox"/> NO  <input type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> <li>Per reviewers, are all parts in English or English translation?</li> </ul> <p><b>If no, explain:</b></p>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> <li>Electronic Submission comments</li> </ul> <p><b>List comments:</b></p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> No comments

<b>CLINICAL</b>  <b>Comments:</b> IR items only for 74-Day letter	<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"> <li>Clinical study site(s) inspections(s) needed?</li> </ul> <p><b>If no, explain:</b></p>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> <li>Advisory Committee Meeting needed?</li> </ul> <p><b>Comments:</b></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"> <li><i>this drug/biologic is not the first in its class</i></li> <li><i>the clinical study design was acceptable</i></li> <li><i>the application did not raise significant safety or efficacy issues</i></li> <li><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></li> </ul>	<input type="checkbox"/> YES Date if known: <input checked="" type="checkbox"/> NO <input type="checkbox"/> To be determined  Reason:
<ul style="list-style-type: none"> <li>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?</li> </ul> <p><b>Comments:</b></p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO
<b>CONTROLLED SUBSTANCE STAFF</b> <ul style="list-style-type: none"> <li>Abuse Liability/Potential</li> </ul> <p><b>Comments:</b></p>	<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
<b>CLINICAL MICROBIOLOGY</b>  <b>Comments:</b>	<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

<b>CLINICAL PHARMACOLOGY</b>  <b>Comments:</b> <ul style="list-style-type: none"> <li>Clinical pharmacology study site(s) inspections(s) needed?</li> </ul>	<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
<b>BIOSTATISTICS</b>  <b>Comments:</b>	<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
<b>NONCLINICAL (PHARMACOLOGY/TOXICOLOGY)</b>  <b>Comments:</b>	<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
<b>PRODUCT QUALITY (CMC)</b>  <b>Comments:</b>	<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
<b><u>New Molecular Entity (NDAs only)</u></b>  <ul style="list-style-type: none"> <li>Is the product an NME?</li> </ul>	<input type="checkbox"/> YES <input type="checkbox"/> NO
<b><u>Environmental Assessment</u></b>  <ul style="list-style-type: none"> <li>Categorical exclusion for environmental assessment (EA) requested?</li> </ul> <p>If no, was a complete EA submitted?</p> <b>Comments:</b>	<input type="checkbox"/> YES <input type="checkbox"/> NO  <input type="checkbox"/> YES <input type="checkbox"/> NO
<b><u>Facility Inspection</u></b>  <ul style="list-style-type: none"> <li>Establishment(s) ready for inspection?</li> </ul> <b>Comments:</b>	<input type="checkbox"/> Not Applicable  <input type="checkbox"/> YES <input type="checkbox"/> NO



<p><b><u>Facility/Microbiology Review (BLAs only)</u></b></p> <p><b>Comments:</b></p>	<p><input type="checkbox"/> Not Applicable</p> <p><input checked="" type="checkbox"/> FILE</p> <p><input type="checkbox"/> REFUSE TO FILE</p> <p><input type="checkbox"/> Review issues for 74-day letter</p>
<p><b><u>CMC Labeling Review (BLAs only)</u></b></p> <p><b>Comments:</b> No issues for 74-Day letter</p>	<p><input type="checkbox"/> Review issues for 74-day letter</p>
<p><b>APPLICATIONS IN THE PROGRAM (PDUFA V) (NME NDAs/Original BLAs)</b></p> <ul style="list-style-type: none"> <li>• 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?</li> <li>• If so, were the late submission components all submitted within 30 days?</li> </ul>	<p><input type="checkbox"/> N/A</p> <p><input checked="" type="checkbox"/> YES</p> <p><input type="checkbox"/> NO</p> <p><input type="checkbox"/> YES</p> <p><input checked="" type="checkbox"/> NO</p>
<ul style="list-style-type: none"> <li>• What late submission components, if any, arrived after 30 days?</li> </ul>	<p>At the August 31, 2016 Pre-BLA Meeting, the applicant agreed to conduct a retrospective evaluation of suicidal ideation and behavior using the Columbia Classification Algorithm of Suicide Assessment (C-CASA) for all subject enrolled in tildrakizumab clinical trials for all indications. The report is to be submitted at the time of the 120 day safety update.</p>
<ul style="list-style-type: none"> <li>• Was the application otherwise complete upon submission, including those applications where there were no agreements regarding late submission components?</li> </ul>	<p><input checked="" type="checkbox"/> YES</p> <p><input type="checkbox"/> NO</p>
<ul style="list-style-type: none"> <li>• Is a comprehensive and readily located list of all clinical sites included or referenced in the application?</li> </ul>	<p><input checked="" type="checkbox"/> YES</p> <p><input type="checkbox"/> NO</p>
<ul style="list-style-type: none"> <li>• Is a comprehensive and readily located list of all manufacturing facilities included or referenced in the application?</li> </ul>	<p><input checked="" type="checkbox"/> YES</p> <p><input type="checkbox"/> NO</p>

REGULATORY PROJECT MANAGEMENT	
<p><b>Signatory Authority:</b> Dr. Beitz, Director, ODE III</p> <p><b>Date of Mid-Cycle Meeting:</b> August 23, 2017 (internal); September 6, 2017 (Mid-cycle communication with applicant)</p> <p><b>21<sup>st</sup> Century Review Milestones (see attached)</b> (listing review milestones in this document is optional):</p> <p><b>Comments:</b></p>	
REGULATORY CONCLUSIONS/DEFICIENCIES	
<input type="checkbox"/>	The application is unsuitable for filing. Explain why:
<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.  <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  <input type="checkbox"/> Priority Review</p>
ACTION ITEMS	
<input checked="" type="checkbox"/>	Ensure that any updates to the review priority (S or P) and classifications/properties are entered into the electronic archive (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 RBPM
<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"/>	If priority review, notify applicant in writing by day 60 (see CST for choices)
<input checked="" type="checkbox"/>	Send review issues/no review issues by day 74
<input checked="" type="checkbox"/>	Conduct a PLR format labeling review and include labeling issues in the 74-day letter
<input checked="" 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: April 2016

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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.**  
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/s/  
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DAWN WILLIAMS  
05/26/2017