

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

761061Orig1s000

OTHER REVIEW(S)

PMR/PMC Development Template

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

BLA # 761061
Product Name: TREMFYA (guselkumab) injection, for subcutaneous use

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

PMR Schedule Milestones:

Initial Protocol Submission:	<u>10/2017</u>
Final Protocol Submission:	<u>04/2018</u>
Trial Completion:	<u>10/2023</u>
Final Report Submission:	<u>04/2024</u>

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

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

Trials in adults with moderate to severe psoriasis are completed and the product is ready for approval. A pharmacokinetics and safety study in pediatric subjects 6 to <18 years of age with moderate to severe psoriasis is needed to ensure that the correct doses are used in the pediatric population and to support extrapolation of efficacy from the adult population. Evaluation of efficacy in pediatric subjects 6 to <18 years of age with moderate to severe psoriasis is performed to support extrapolation of efficacy from the adult population.

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

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

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

If not a PMR, skip to 4.

- **Which regulation?**

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

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

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

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

- Analysis of spontaneous postmarketing adverse events?
Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk

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

- Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk

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

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

Conduct a 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 guselkumab of at least one year).

Required

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

Continuation of Question 4

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

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

Agreed upon:

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

Other

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

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

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

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

PMR/PMC Development Coordinator:

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

(signature line for BLAs)

PMR/PMC Development Template

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

BLA # 761061

Product Name: TREMFYA (guselkumab) injection, for subcutaneous use

PMR Description: A prospective, registry based observational exposure cohort study that compares the maternal, fetal, and infant outcomes of women exposed to guselkumab 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.

PMR Schedule Milestones:	Final Protocol Submission:	<u>01/2018</u>
	Trial Completion:	<u>12/2025</u>
	Final Report Submission:	<u>12/2026</u>

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

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

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 are needed in this population.

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

Moderate to severe psoriasis occurs in women of child bearing age. Therefore, we expect there will be some exposure of pregnant women to guselkumab. Data on use of guselkumab in pregnant women are needed

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

If not a PMR, skip to 4.

– **Which regulation?**

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

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

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

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

Analysis of spontaneous postmarketing adverse events?

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

Analysis using pharmacovigilance system?

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

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

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

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

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

A prospective, registry based observational exposure cohort study in pregnant women and neonates.

Required

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

Continuation of Question 4

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

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

Agreed upon:

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

-
- Other
-

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

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

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

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

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

PMR/PMC Development Coordinator:

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

(signature line for BLAs)

Moderate to severe psoriasis occurs in females of child bearing age. Therefore we expect there will be some exposure of pregnant women. Data on use of guselkumab in pregnant women are needed.

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

If not a PMR, skip to 4.

- **Which regulation?**

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

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

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

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

- Analysis of spontaneous postmarketing adverse events?

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

- Analysis using pharmacovigilance system?

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

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

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

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

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

A retrospective cohort study using claims or electronic medical record data or a case control study

Required

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

Continuation of Question 4

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

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

Agreed upon:

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

-
- Other
-

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

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

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

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

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

PMR/PMC Development Coordinator:

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

(signature line for BLAs)

PMR/PMC Development Template

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

BLA # 761061

Product Name: TREMFYA (guselkumab) injection, for subcutaneous use

PMR Description: Conduct an observational study to assess the long-term safety of guselkumab 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 guselkumab-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 guselkumab-exposed and comparator(s) cohorts, clearly define the study drug initiation period and any exclusion and inclusion criteria. Enroll patients over an initial 6 year period and follow for a minimum of 8 years from the time of enrollment.

PMR Schedule Milestones:	Initial Protocol Submission:	<u>12/2017</u>
	Final Protocol Submission:	<u>12/2018</u>
	Study Completion:	<u>12/2030</u>
	Final Report Submission:	<u>12/2031</u>

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

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

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. The safety profile has been adequately assessed in the pre-approval program. However, the recommended PMR is to evaluate the occurrence of long-latency safety outcomes, including malignancy that cannot be adequately assessed in the clinical trial program. A PMR study would also allow for the evaluation of safety events which occur infrequently, such as serious infections.

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

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

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

– **Which regulation?**

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

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

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

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

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

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

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

This is an observational study to collect additional data on long-term safety.

Required

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

Continuation of Question 4

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

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

Agreed upon:

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

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

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

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

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

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

PMR/PMC Development Coordinator:

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

(signature line for BLAs)

PMR/PMC Development Template: Product Quality (CMC)

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

BLA # 761061
Product Name: TREMFYA (guselkumab) injection, for subcutaneous use

PMC Description: Perform a leachable study to evaluate the drug product container closure system through the end of shelf-life when stored under the recommended conditions. Testing will be performed at regular intervals and will include appropriate methods to detect, identify, and quantify organic non-volatile (e.g., HPLC-UV-MS), volatile (e.g., headspace GC-MS) and semi-volatile (e.g., GC-MS) species and metals (e.g., ICP-MS). Study results will be updated annually in the BLA Annual Report. The complete data and risk evaluation for potential impact of leachables on product safety and quality will be submitted to the BLA.

PMC Schedule Milestones: Final Protocol Submission: 09/2017
Study Completion: 01/2020
Final Report Submission: 06/2020

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

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

The results from the extractables and leachables studies that have been performed and the clinical studies indicate that the presence of leachates from the guselkumab commercial container closure system does not appear to be a significant safety or product quality issue. However, a comprehensive real-time leachable study through the end of drug product expiry period was not performed.

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

The leachables study for guselkumab is currently incomplete. The real-time leachable study that was performed did not assess volatile leachables and appears to only include an evaluation of compounds identified in the extractable studies, rather than all potential leachables. Additionally, the study was conducted only up to 6 months and no additional data were available to assess potential leachables through the end of drug product shelf-life. A complete leachable study including the evaluation of all potential volatile organic, semi-volatile organic, non-volatile organic and inorganic compounds through the end of drug product shelf-life should be performed to enable a risk evaluation of potential impact to safety and product quality.

3. [OMIT – for PMRs only]
4. What type of study is agreed upon (describe and check type below)?

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

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

Describe the agreed-upon study:

Conduct a leachable study through the 24 month shelf-life using the drug product container closure system using methods to detect, identify, and quantify organic non-volatile compounds, volatile compounds, semi-volatile compounds, and metal species and evaluate the impact of leachables to product safety and quality.

5. To be completed by ONDQA/OBP Manager:

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

PMR/PMC Development Coordinator:

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

(signature line for BLAs only)

PMR/PMC Development Template

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

BLA # 761061
Product Name: TREMFYA (guselkumab) injection, for subcutaneous use

PMC Description: Provide additional data comparing the (b) (4)
(b) (4). Include the (b) (4) in the (b) (4)
revalidation program if the new information indicates that the (b) (4)
(b) (4).

PMC Schedule Milestones: Study Completion: 04/2018
Final Report Submission: 06/2018

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

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

The sponsor needs to conduct more studies to compare the (b) (4)

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



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

If not a PMR, skip to 4.

– **Which regulation?**

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

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

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

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

- Analysis of spontaneous postmarketing adverse events?

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

- Analysis using pharmacovigilance system?

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

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

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

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

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

Provide additional data comparing the	(b) (4)		
(b) (4)	Include the	(b) (4)	in the
(b) (4)	revalidation program if the new information indicates that the	(b) (4)	.

Required

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

Continuation of Question 4

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

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

Agreed upon:

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

-
- Other
-

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

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

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

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

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

PMR/PMC Development Coordinator:

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

(signature line for BLAs)

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/s/

MATTHEW E WHITE
06/22/2017

TATIANA OUSSOVA
06/23/2017

Clinical Inspection Summary

Date	June 1, 2017
From	Roy Blay, Ph.D., Reviewer Good Clinical Practice Assessment Branch Division of Clinical Compliance Evaluation Office of Scientific Investigations (OSI)
To	Matthew White, RPM Kevin Clark\Melinda McCord, Clinical Reviewers Gordana Diglisic, Clinical Team Leader Division of Dermatology and Dental Products (DDDP)
BLA #	761061
Applicant	Janssen Biotech, Inc.
Drug	Guselkumab
NME	Yes
Therapeutic Classification	Priority Review
Proposed Indication	Treatment of moderate to severe plaque psoriasis
Consultation Request Date	December 8, 2016
Summary Goal Date	June 9, 2017
Action Goal Date	June 30, 2017
PDUFA Date	July 16, 2017

1. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

The clinical sites of Drs. Bhutani, Katarzyna, and Tsen-Fang were inspected in support of this NDA. Based on the results of these inspections, the studies appear to have been conducted adequately, and the data generated by these sites appear acceptable in support of the respective indication.

The final classification of the inspection of Dr. Bhutani was No Action Indicated (NAI). The classification of the inspections of Drs. Katarzyna and Tsen-Fang are (b) (5), pending receipt and review of the inspection reports and final classification.

2. BACKGROUND

The Applicant submitted this BLA to support the use of guselkumab in the treatment of moderate to severe plaque psoriasis.

Inspections were requested for the following protocols in support of this application:

Protocol CNTO1959PSO3001

This was a Phase 3, randomized, double-blind, multicenter, placebo- and active comparator-controlled study evaluating the safety and efficacy of guselkumab in subjects with moderate to severe plaque-type psoriasis.

The double-blind treatment period extended from Week 0 through Week 44. At Week 0, subjects who satisfied all inclusion and exclusion criteria were randomized in a 2:1:2 ratio to 1 of 3 treatment groups. Group I received guselkumab 100 mg at Weeks 0, 4, and 12, and every 8 weeks (q8w) thereafter through Week 44. Group II received placebo beginning at Week 0 followed by guselkumab 100 mg at Weeks 16 and 20 and q8w thereafter through Week 44. Group III received adalimumab 80 mg at Week 0 followed by adalimumab 40 mg at Week 1 and every 2 weeks (q2w) thereafter through Week 47. An open-label guselkumab treatment period began after Week 48 and extended through Week 160.

The two co-primary endpoints of this study were:

- The number and proportion of subjects who achieved an Investigator's Global Assessment (IGA) score of cleared (0) or minimal (1) at Week 16, comparing the guselkumab group and the placebo group
- The number and proportion of subjects who achieved a Psoriasis Area and Severity Index (PASI) 90 response at Week 16, comparing the guselkumab group and the placebo group

Protocol CNTO1959PSO3001 was conducted at 101 sites in ten countries with an enrollment of 837 subjects in the study.

Protocol CNTO1959PSP3002

This was a Phase 3, randomized, double-blind, multicenter, placebo- and active comparator-controlled study of guselkumab in subjects with moderate to severe plaque-type psoriasis with randomized withdrawal and retreatment.

At Week 0, subjects who satisfied all inclusion and exclusion criteria were randomized in a 2:1:1 ratio to 1 of 3 arms. Group I received guselkumab 100 mg at Weeks 0, 4, 12, and 20. Group II received placebo beginning at Week 0 followed by guselkumab 100 mg at Weeks 16 and 20. Group III received adalimumab 80 mg at Week 0 followed by adalimumab 40 mg at Week 1 and every 2 weeks (q2w) thereafter through Week 23. Subjects self-administered the study agent at home through Week 23. No study agent was administered from Week 23 to Week 28.

Beginning at Week 28, therapy for all subjects was based on their level of response at that visit, with some subjects undergoing randomized withdrawal and retreatment. The open-label guselkumab treatment period began at Week 76 and extended through Week 160.

The co-primary endpoints in this study were:

- The proportion of subjects who achieved an IGA score of cleared (0) or minimal (1) at Week 16, comparing the guselkumab group and the placebo group
- The proportion of subjects who achieved a PASI 90 response at Week 16, comparing the guselkumab group and the placebo group

Protocol CNTO1959PSP3002 was conducted at 115 sites in nine countries with an enrollment of 993 subjects in the study.

Protocol CNTO1959PSP3003

This was a Phase 3, randomized, double-blind, multicenter study. Subjects received open-label ustekinumab 45 mg or 90 mg (according to the subject's baseline [Week 0] weight) at Weeks 0 and 4. At Week 16, subjects were to be assessed for efficacy according to the IGA, which determined their subsequent treatment through Week 44: subjects with IGA \geq 2 were randomized to either switch to guselkumab 100 mg at Weeks 16 and 20 and then every 8 weeks (q8w) thereafter or continue on ustekinumab every 12 weeks (q12w); subjects with an IGA=0 or 1 were to continue to receive open-label ustekinumab q12w.

Starting at Week 16, visits for randomized subjects were every 4 weeks (q4w) through Week 44; visits for subjects who continued on open-label ustekinumab were to be q12w through Week 40 (i.e., ustekinumab administration visits). All subjects were to have an additional follow-up visit at Week 52 and a final safety visit at Week 60.

The primary endpoint was the number of visits at which subjects achieved an IGA response of cleared (0) or minimal (1) and at least a 2-grade improvement (from Week 16) between Week 28 and Week 40 among randomized subjects with an inadequate (IGA \geq 2) response to ustekinumab at Week 16.

Protocol CNTO1959PSP3003 was conducted at 100 sites in ten countries with an enrollment of 871 subjects in the study.

Rationale for Site Selection

The clinical site of Dr. Bhutani (Protocol -3001) was selected for inspection because of a discrepancy between the co-primary efficacy endpoints for the adalimumab arm (100% of subjects had an IGA score of 0 or 1 but 0% achieved a PASI 90 response). This site also had protocol violations related to receiving treatment out of order.

The clinical site of Dr. Tsen-Fang was selected for inspection because of relatively high enrollment numbers. In addition, Dr. Tsen-Fang conducted two pivotal protocols (-3001 and -3003).

The clinical site of Dr. Katarzyna (Protocol -3002) was selected for inspection because of the relatively large number of subjects enrolled, in addition to a much lower than average response rate (IGA score of 0 or 1) for adalimumab (20%). This site also had protocol violations related to the start of the maintenance period.

3. RESULTS (by site):

Site #/ Name of CI/ Address	Protocol #/ # of Subjects (enrolled)	Inspection Dates	Classification
US93367 Tina Bhutani, M.D. The Regents of the University of CA 185 Berry Street San Francisco, CA, 94107	CNTO1959PSO3001/ 14	4-6 April 2017	NAI
PL00239 Łoza Katarzyna, M.D. Miedzyleski Szpital Specjalistyczny Ul Bursztynowa 2 Warszawa, 04-749 Poland	CNTO1959PSP3002/ 19	(b) (5)	(b) (5) Pending final classification
TW00035 Tsen-Fang Tsai, M.D. National Taiwan University Hospital 7, Chung-Shan South Road, Taipei, 10002 Taiwan	CNTO1959PSO3003/ 14	(b) (5)	(b) (5) Pending final classification

Key to Compliance Classifications

NAI = No deviation from regulations.

VAI = Deviation(s) from regulations.

OAI = Significant deviations from regulations. Data unreliable.

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

1. Tina Bhutani, M.D.

At this site for Protocol CNTO1959 PSO3001, 18 subjects were screened for the study, three subjects failed screening, and one subject withdrew consent.

For all 18 subjects enrolled, the following was reviewed:

- That informed consent was obtained prior to conducting study procedures
- Final disposition
- Serious adverse events, if any.

Dr. Bhutani verbally confirmed that no subject at her site experienced a serious adverse event, which was consistent with data listings.

For 14 out of 14 subjects who were exposed to investigational product (IP), the following data was validated (with source documents compared to data listings):

- Baseline: IGA, PASI, and ss-IGA
- Week 16: IGA, PASI, ss-IGA, and DLQI
- Week 24: IGA and PASI
- Week 48 IGA and PASI

For 5 out of the 14 subjects exposed to investigational product (IP), in addition to the efficacy endpoints listed above, the following was reviewed:

- Eligibility
- Adherence to the protocol, including review of prior therapy and concomitant medications
- Concomitant medications in the source data as compared to the data listings
- Adverse events/serious adverse events in the source data as compared to the data listings
- Adequacy of documentation of drug accountability

A Form FDA 483 was not issued at the conclusion of the inspection. This study appears to have been conducted adequately, and the data generated by this site appear acceptable in support of the respective indication.

2. Łoza Katarzyna, M.D.

At this site for Protocol CNTO1959PSP3002, 21 subjects were screened, 19 subjects were enrolled, and 18 subjects completed the study.

The study records of the 19 enrolled subjects were reviewed for this protocol. The primary efficacy endpoints (IGA scores and PASI 90 at Week 16) were verified for all subjects. There was no evidence of under-reporting of adverse events.

A Form FDA 483 was not issued at the conclusion of the inspection. This study appears to have been conducted adequately, and the data generated by this site appear acceptable in support of the respective indication.

3. Tsen-Fang Tsai, M.D.

At this site for Protocol CNTO1959PSO3003, 27 subjects were screened, 23 subjects were enrolled in the study, and 22 subjects completed the study.

The records of the 14 subjects were reviewed. The records appeared adequate, the primary efficacy endpoint was verifiable, and no major protocol violations were noted.

A Form FDA 483 was not issued at the conclusion of the inspection. This study appears to have been conducted adequately, and the data generated by this site appear acceptable in support of the respective indication.

{See appended electronic signature page}

Roy Blay, Ph.D.
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

CONCURRENCE:

{See appended electronic signature page}

Phillip Kronstein, M.D.
Team Leader
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

CONCURRENCE:

{See appended electronic signature page}

Kassa Ayalew, M.D., M.P.H
Branch Chief
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

cc:

Central Doc. Rm.\BLA 761061

DDDP\Division Director\Kendall Marcus

DDDP\Team Leader\Gordana Diglisic

DDDP\Medical Officer\Kevin Clark\Melinda McCord

DDDP\Project Manager\Matthew White

OSI\DCCE\Division Director\Ni Khin

OSI\DCCE\GCPAB\Branch Chief\Kassa Ayalew

OSI\DCCE\GCPAB\Team Leader\Phillip Kronstein

OSI\DCCE\GCPAB\Reviewer\Roy Blay

OSI\DCCE\Program Analysts\Joseph Peacock\Yolanda Patague

OSI\Database Project Manager\Dana Walters

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/s/

ROY A BLAY
05/31/2017

PHILLIP D KRONSTEIN
05/31/2017

KASSA AYALEW
06/01/2017



Center for Drug Evaluation and Research
Office of Pharmaceutical Quality
Office of Biotechnology Products

LABELS AND LABELING REVIEW

Date:	May 31, 2017
Reviewer:	Vicky Borders-Hemphill, PharmD Labeling Review Specialist Office of Biotechnology Products (OBP)
Through:	Willie Wilson, PhD, Product Quality Reviewer OBP/Division of Biotechnology Review and Research I
Application:	BLA 761061
Product:	Tremfya (guselkumab)
Applicant:	Janssen Biotech, Inc.
Submission Date(s):	November 16, 2016, May 24, 2017, and May 30, 2017

I) RECOMMENDATION

The labels and labeling for Tremfya (guselkumab) Injection, 100 mg/mL in a prefilled syringe for subcutaneous use submitted on May 24, 2017, and May 30, 2017 are acceptable from a quality perspective.

II) BACKGROUND AND SUMMARY DESCRIPTION

The Applicant submitted BLA 761061 Tremfya (guselkumab) on November 16, 2016, which provides for the treatment of adults with moderate-to-severe plaque psoriasis who are candidates for systemic therapy or phototherapy.

Table 1: Proposed Product Characteristics of Tremfya (guselkumab).

Proprietary Name:	Tremfya
Nonproprietary Name:	guselkumab
Dosage Form:	Injection
Strength and Container-Closure:	100 mg/mL in a prefilled syringe (PFS)
Route of Administration:	Subcutaneous
Storage and Handling:	Store in a refrigerator at 2°C to 8°C (36°F to 46°F). Store in original carton until time of use. Protect from light until use. Do not freeze. Do not shake.
Indication:	treatment of adults with moderate-to-severe plaque psoriasis who are candidates for systemic therapy or phototherapy
Dose and Frequency:	100 mg at Week 0, Week 4, and every 8 weeks thereafter

III) MATERIALS REVIEWED

We considered the materials listed in Table 2 for this review.

Table 2: Materials Considered for this Label and Labeling Review

Materials Reviewed	Appendix Section
Proposed Labels and Labeling	A
Other	B
Relevant Code of Federal Regulations and CDER Labeling Best Practices	C
Acceptable Labels and Labeling	D

n/a = not applicable for this review

IV) DISCUSSION

The proposed labels were evaluated for compliance to the applicable code of federal regulations and CDER Labeling Best Practices (see Appendix C).

V) CONCLUSION

The prescribing information, instructions for use, container labels, and carton labeling for Tremfya (guselkumab) Injection, 100 mg/mL in a prefilled syringe for subcutaneous use were reviewed and found to comply with the following regulations: 21 CFR 610.60 through 21 CFR 610.67; 21 CFR 201.2 through 21 CFR 201.25; 21 CFR 201.50 through 21 CFR 201.57; 21 CFR 201.100 and United States Pharmacopeia (USP). The labels and labeling submitted on May 24 and May 30, 2017 are acceptable (see Appendix D) from a quality perspective.

APPENDICES

Appendix A: Proposed Labeling

- Prescribing Information and Medication Guide
(\\cdsesub1\evsprod\bla761061\0000\m1\us\annotated-draft-labeling-text.pdf)
- Instructions for Use (\\cdsesub1\evsprod\bla761061\0000\m1\us\ifu-pfs-u.pdf)
- Container Labels

(b) (4)



Appendix B: Other

Appendix C: Applicant Code of Federal Regulations and CDER Best Labeling Practices

Table 3: Label^{1,2} and Labeling³ Standards

Container⁴ Label Evaluation

Regulations	Conforms			Comments and Recommendations
	Yes	No	n/a	
<u>Proper Name</u> 21 CFR 610.60 21CFR 201.10			x	This is considered a partial label. See assessment under partial label below.
<u>Manufacturer name, address, and license number</u> 21 CFR 610.60			x	This is considered a partial label. See assessment under partial label below.
<u>Lot number or other lot identification</u> 21 CFR 610.60 21 CFR 201.18 21CFR 201.100			x	This is considered a partial label. See assessment under partial label below.
<u>Expiration date</u> 21 CFR 610.60 21 CFR 201.17			x	This is considered a partial label. See assessment under partial label below.
<u>Multiple dose containers (recommended individual dose)</u> 21 CFR 610.60			x	single dose prefilled syringe
<u>Statement: "Rx only"</u> 21 CFR 610.60	x			

¹ Per 21 CFR 1.3 (b) *Label* means any display of written, printed, or graphic matter on the immediate container of any article, or any such matter affixed to any consumer commodity or affixed to or appearing upon a package containing any consumer commodity.

² Per CFR 600.3(dd) *Label* means any written, printed, or graphic matter on the container or package or any such matter clearly visible through the immediate carton, receptacle, or wrapper.

³ Per 21 CFR 1.3(a) *Labeling* includes all written, printed, or graphic matter accompanying an article at any time while such article is in interstate commerce or held for sale after shipment or delivery in interstate commerce.

⁴ Per 21 CFR 600.3(bb) *Container* (referred to also as "final container") is the immediate unit, bottle, vial, ampule, tube, or other receptacle containing the product as distributed for sale, barter, or exchange.

Regulations	Conforms			Comments and Recommendations
	Yes	No	n/a	
21 CFR 201.100				
<u>Medication Guide</u> 21 CFR 610.60			x	We consider this to be a partial label thus the MG statement shall be placed on the carton labeling. See carton labeling assessment below.
<u>No Package for container</u> 21 CFR 610.60			x	
<u>Partial label</u> 21 CFR 610.60 21 CFR 201.10	x			
<u>No container label</u> 21 CFR 610.60			x	
<u>Visual inspection</u> 21 CFR 610.60	x			Confirm there is sufficient area on the container to allow for visual inspection when the label is affixed to the container. <i>The Applicant confirms there is appropriate area to allow for visual inspection</i>
<u>NDC numbers</u> 21 CFR 201.2 21CFR 207.35	x			
<u>Route of administration</u> 21 CFR 201.5 21 CFR 201.100	x			
<u>Preparation instructions</u> 21 CFR 201.5	x			If space permits, consider adding the statement "Discard unused portion" to appear under the "single-Dose" statement. <i>Applicant revised as requested</i>
<u>Package type term</u> 21 CFR 201.5	x			
<u>Drugs Misleading statements</u> 21 CFR 201.6	x			
<u>Strength</u> 21 CFR 201.10 21CFR 201.100	x			

Regulations	Conforms			Comments and Recommendations
	Yes	No	n/a	
<u>Drugs Prominence of required label statements</u> 21 CFR 201.15	X			
<u>Bar code label requirements</u> 21 CFR 201.25 21CFR 610.67	X			Ensure there is adequate white space around the linear bar code to facilitate scanning. <i>The Applicant confirms there is adequate white space around the linear barcode to facilitate scanning</i>
<u>Net quantity</u> 21 CFR 201.51	X			
<u>Usual dosage statement</u> 21 CFR 201.55 21CFR 201.100			X	This is considered a partial label, thus this information must appear on the carton, PI, and IFU (if applicable). See carton assessment below.
<u>Inactive ingredients</u> 21 CFR 201.100			X	We consider this to be a partial label, thus this information must appear on the carton, PI, and IFU (if applicable). See carton labeling assessment below.
<u>Storage requirements</u>			X	We consider this to be a partial label, thus this information must appear on the carton, PI, and IFU (if applicable). See carton labeling assessment below.
<u>Dispensing container</u> 21 CFR 201.100			X	

Package Label⁵ Evaluation

Regulations	Comply			Comments and Recommendations
	Yes	No	n/a	
<u>Proper name</u> 21CFR 610.61	X			See DMEPA review regarding approving the proper name as designated without a suffix. ⁶

⁵ Per 21 CFR 600.3(cc) *Package* means the immediate carton, receptacle, or wrapper, including all labeling matter therein and thereon, and the contents of the one or more enclosed containers. If no package, as defined in the preceding sentence, is used, the container shall be deemed to be the package. Thus this includes the carton, prescribing information, and patient labeling.

⁶ Mena-Grillasca C. BLA 761061 Tremfya (guselkumab) Human Factors, Label, Labeling, and Packaging Review. Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2017 May 12; RCM 2016-2621 and 2016-2649.

Regulations	Comply			Comments and Recommendations
	Yes	No	n/a	
21 CFR 201.50 21CFR 201.10				
<u>Manufacturer name, address, and license number</u> 21CFR 610.61	x			
<u>Lot number or other lot identification</u> 21CFR 610.61	x			
<u>Expiration date</u> 21CFR 610.61 21 CFR 201.17	x			
<u>Preservative</u> 21CFR 610.61	x			
<u>Number of containers</u> 21CFR 610.61	x			
<u>Strength/volume</u> 21CFR 610.61 21 CFR 201.10 21 CFR 201.100	x			
<u>Storage temperature</u> 21CFR 610.61	x			
<u>Handling: "Shake Well", "Do not Freeze" or equivalent</u> 21CFR 610.61	x			
<u>Multiple dose containers (recommended individual dose)</u> 21CFR 610.61			x	
<u>Route of administration</u> 21CFR 610.61	x			

Regulations	Comply			Comments and Recommendations
	Yes	No	n/a	
<u>Known sensitizing substances</u> 21CFR 610.61	x			
<u>Antibiotics added during manufacturing</u> 21CFR 610.61	x			
<u>Inactive ingredients</u> 21CFR 610.61 21 CFR 201.100		x		Revise the list of ingredients statement to read as follows: "Each single-dose prefilled syringe delivers 100 mg guselkumab in 1 mL which contains L-histidine (0.6 mg), L-histidine monohydrochloride monohydrate (1.5 mg), polysorbate 80 (0.5 mg), sucrose (79 mg), and Water for Injection, USP. Contains no preservative. No U.S. standard of potency." providing the deliverable volume of the prefilled syringe and placing the inactive ingredients in alphabetical order per USP <1091> Labeling of Inactive Ingredients. <i>Applicant revised as requested</i>
<u>Adjuvant, if present</u> 21CFR 610.61	x			
<u>Source of the product</u> 21CFR 610.61	x			
<u>Identity of each microorganism used in manufacturing</u> 21CFR 610.61 (q)	x			"Guselkumab is produced in a mammalian cell line using recombinant DNA technology." is provided in PI section 11
<u>Minimum potency of product</u> 21CFR 610.61	x			
<u>Rx only</u> 21CFR 610.61	x			
<u>Divided manufacturing</u>			x	

Regulations	Comply			Comments and Recommendations
	Yes	No	n/a	
21 CFR 610.63				
<u>Distributor</u> 21 CFR 610.64			x	
<u>Bar code</u> 21 CFR 610.67 21 CFR 201.25	x			
<u>NDC numbers</u> 21 CFR 201.2 21CFR 207.35	x			
<u>Route of administration</u> 21 CFR 201.5 21 CFR 201.100	x			
<u>Preparation instructions</u> 21 CFR 201.5	x			
<u>Package type term</u> 21 CFR 201.5	x			
<u>Drugs Misleading statements</u> 21 CFR 201.6	x			
<u>Drugs Prominence of required label statements</u> 21 CFR 201.15	x			
<u>Net quantity</u> 21 CFR 201.51	x			
<u>Usual dosage statement</u> 21 CFR 201.55 21 CFR 201.100	x			
<u>Dispensing container</u> 21 CFR 201.100			x	
<u>Medication Guide</u>	x			conforms

Regulations	Comply			Comments and Recommendations
	Yes	No	n/a	
21 CFR 610.60				

Prescribing Information and Patient Labeling Evaluation

Labeling Standards	Comply			Comments and Recommendations
	Yes	No	n/a	
PRESCRIBING INFORMATION				
Highlights of prescribing information				
PRODUCT TITLE 21 CFR 201.57(a)(2)	x			
DOSAGE AND ADMINISTRATION 21 CFR 201.57(a)(7)	x			
DOSAGE FORMS AND STRENGTHS 21 CFR 201.57(a)(8)	x			There is only one configuration, therefore the bullet and duplicate Prefilled Syringe is not needed. <i>The Applicant accepted our revisions</i>
Full Prescribing Information				
2 DOSAGE AND ADMINISTRATION 21 CFR 201.57(c)(3)	x			
3 DOSAGE FORMS AND STRENGTHS 21 CFR 201.57(c)(4)		x		Revise (b) (4) to single dose for consistency with container labels and carton labeling and to comply with draft guidance for industry, Selection of the Appropriate Package Type Terms and Recommendations for Labeling Injectable Medical Products Packaged in Multiple-Dose, Single-Dose, and Single-Patient-Use Containers for Human Use, the appropriate term is single-dose (intended for single use for one patient), revise the package type term to single-dose throughout all labeling. <i>The Applicant accepted our revisions</i>
6.2 IMMUNOGENICITY		x		Revise section 6.2 so that the standard statement appears as the first paragraph according to OND best labeling practices. <i>The Applicant accepted our revisions</i>
11 DESCRIPTION 21 CFR		x		We edited the dosage form to match the presentation in USP General Chapters: <1>

Labeling Standards	Comply			Comments and Recommendations
	Yes	No	n/a	
201.57(c)(12)				<p>Injections. Note the presentation as "injection" in the product title in the highlights section is an acceptable difference.</p> <p><input type="checkbox"/> [DRUG] Injection—Liquid preparations that are drug substances or solutions thereof.</p> <p><input type="checkbox"/> [DRUG] for Injection—Dry solids that, upon the addition of suitable vehicles, yield solutions conforming in all respects to the requirements for Injections.</p> <p><i>The Applicant accepted our revisions</i></p>
16 HOW SUPPLIED/ STORAGE AND HANDLING 21 CFR 201.57(c)(17)		x		<p>Revise the section to include the proper name, and strength per total volume. The dosage forms and strengths should be consistent with the container/carton labeling.</p> <p><i>The Applicant accepted our revisions</i></p>
Manufacturer information For BLAs: 21 CFR 610.61, 21 CFR 610.64 For NDAs: 21 CFR 201.1		x		<p>We added the license number to comply with 21 CFR 610.61(b). We note inclusion of (b) (4) (b) (4) (b) (4) which we find does not fulfill the aforementioned CFR because (b) (4) (b) (4)</p> <p><i>The Applicant accepted our revisions</i></p>
MEDICATION GUIDE, INSTRUCTIONS FOR USE, AND PATIENT INFORMATION				
Title (names and dosage form)	x			
Storage and Handling	x			
Ingredients	x			
Manufacturer Information 21 CFR 610.61 21 CFR 610.64	x			

APPENDIX D. Acceptable Labels and Labeling

- Prescribing Information (submitted 24May17
\\cdsesub1\evsprod\bla761061\0039\m1\us\draft-labeling-text.doc)
- Instructions for Use (submitted 24May17
\\cdsesub1\evsprod\bla761061\0039\m1\us\ifu-pfs-u.doc)
- Container Labels (submitted 30May17)

(b) (4)



- Carton Labeling (submitted 30May17)

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*****

Date of This Review: May 12, 2017

Requesting Office or Division: Division of Dermatology and Dental Products (DDDP)

Application Type and Number: BLA 761061

Product Name and Strength: Tremfya
(guselkumab)
Injection
100 mg/mL Prefilled Syringe (PFS)

Product Type: Single Ingredient, Combination Product

Rx or OTC: Rx

Applicant/Sponsor Name: Janssen Biotech, Inc.

Submission Date: November 16, 2016

OSE RCM #: 2016-2621 and 2016-2649

DMEPA Primary Reviewer: Carlos M Mena-Grillasca, RPh

DMEPA Acting Team Leader: Sarah K. Vee, PharmD

DMEPA Associate Director for Human Factors: QuynhNhu Nguyen, MS

OMEPRM Acting Deputy Director: Lubna Merchant, MS, PharmD

1 REASON FOR REVIEW

This review evaluates the human factors (HF) validation study report, the proposed container label, carton labeling, Prescribing Information (PI), and Instructions for Use (IFU) for Tremfya (guselkumab) injection (BLA 761061), in response to consults from the Division of Dermatology and Dental Products (DDDP). The Applicant submitted BLA 761061, a 351(a) application, on November 16, 2016 for a prefilled syringe containing Tremfya (guselkumab), intended to treat moderate to severe plaque psoriasis. BLA 761061 was granted priority review designation by the Agency.

2 MATERIALS REVIEWED

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

Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
Previous DMEPA Reviews	B
Human Factors Study	C
ISMP Newsletters	D (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 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

The Applicant submitted two Human Factors studies:

1. A Summative Usability Study Report from October 2012 to validate the (b) (4) (PFS) for a broad user base across two different drug viscosities. The user population covered in the study included patients with Rheumatoid Arthritis (RA), Psoriasis or Crohn's disease, caregivers, and Healthcare Providers (HCP). We note that on an Advice Letter to the Applicant¹ dated July 7, 2014, CDRH agreed that the Applicant could leverage data from previous Human Factor studies. DMEPA was not involved in those earlier communications. Furthermore, DMEPA did not request Human Factor studies for the standard prefilled syringe.

A total of 60 participants participated in the Human Factors validation studies. The study design included 30 injection naïve participants (n=15 Psoriasis or Crohn's patients and n=15 Caregivers) and 30 injection experienced participants (n=15 RA patients and 15 HCP).

¹ Marcus, K. Advice Letter for Guselkumab (IND 105004). Silver Spring (MD): FDA, CDER, ODE III, DDDP, (US); 2014 Jul 7.

All injection naïve participants received training during the first session, prior to the first supervised injection (injection #1). One week later, the injection naïve participants performed an unaided injection (injection #2) followed by an unaided injection of the opposite high (8 cP) or low (2 cP) viscosity (injection #3).

All injection experienced participants were self-trained and performed three unaided injections. DMEPA submitted an Information Request to the Applicant requesting clarification on the extent of the self-training and their rationale as to why it is reflective of real world use. The Applicant explained that during the Session Overview for the injection experienced participants, the moderator explained the purpose of the study, subsequently telling the participants “You will receive the instructions that come with the product and you will self-train by reading them”. The Applicant proposed that this is consistent with real-world use as the IFU states “If your doctor decides that you or a caregiver may be able to give your injections of TRADENAME at home, you should receive training on the right way to prepare and inject TRADENAME using the prefilled syringe before attempting to inject.” However, the Applicant acknowledges that the real-world scenario may differ from this recommendation. They argue that the packaging is designed “such that the IFU appears on top of the PFS (b) (4) when the user opens the packaging. The IFU is the first thing that the user encounters and it is provided in a pictorial format to facilitate correct use. Even upon encountering the IFU, however, users may choose to read it or not. This real-world scenario is thus represented in the Injection Experienced group with self-training in the HFS. For this group, the moderator presented the IFU to the participant (much the same way that the packaging presents the IFU to the user), but the participant was not required to read it prior to the injection. Additionally, in the same way that HFS participants had access to the IFU during their injections, all users will have the IFU available for reference during their injections in the home setting. The Injection Experienced group was intended to represent a worst-case scenario of user training.” We acknowledge that the participants were given the IFU, however, by prompting the participants with the statement “you will self-train by reading them (referring to the IFU)”, the participants might have felt that they were expected to read the IFU, whereas they might choose not to read the IFU at home in a real-world scenario. During the first injection 28/30 injection naïve participants and 15/30 injection experienced participants referenced the IFU. During the second injection 29/30 injection naïve participants and 9/30 injection experienced participants referenced the IFU.

The following table summarize the use-related errors.

Task	Injection Naïve	Injection Experience
Pinch the skin	2 errors*	8 errors*
Activate safety mechanism	0 errors	2 errors (1 RA patient; 1 Psoriasis patient)

* No details or root cause analysis performed for these use errors.

We note that the applicant did not further investigate errors related to failure to pinch the skin during the injection. Although there are no safety concerns associated with failure to pinch the skin, there may be a concern for diminished efficacy due to the potential for an intramuscular instead of subcutaneous injection.

Two participants failed to activate the safety mechanism during the high viscosity injection. Nonetheless, the full dose was delivered. In addition, both participants successfully completed

the injection (i.e. full dose delivered and safety mechanism activated) during the low viscosity injection. Root cause analysis revealed that one participant's severe RA in her hands, coupled with the high viscosity injection, might have contributed to the failure to complete the final press needed at the end of the plunger travel in order to activate the safety mechanism. The other participant was using a unique hand posture, with the thumb overlapping the plunger pad. The orientation of the injection skin pad and the higher viscosity, coupled with the hand posture might have contributed to the use error. The risk of not activating the safety guard is a needle stick injury. However, all participants knew how to dispose of the syringe after injection. We do not have any recommendations at this time.

Our evaluation of these errors indicate that they are associated with first time use of injectable products administered via PFS. In addition, the study results showed that failure to activate the safety mechanism use errors did not reoccur as end users were able to complete a successful injection at the lower viscosity injections (2 cP). Tremfya's target viscosity is near the lower end at (b) (4), which might help minimize these errors. Our evaluation of the risks associated with the use of the proposed product did not identify any new or unique risks for the proposed product. As such, we do not have any additional recommendations at this time to further mitigate the observed errors.

2.



Proposed Container Label and Carton Labeling

In addition to the HF validation study evaluation, our review of the proposed IFU did not identify any additional concerns from a medication errors perspective. Furthermore, our review of the proposed container label and carton labeling did not identify safety concerns. However, we have three recommendations provided in Section 4.1 to improve the container labels and carton labeling.

Nonproprietary Name

Finally, we note that FDA recently issued a final guidance entitled *Nonproprietary Naming of Biological Products* on January 13, 2017 stating the Agency's intention to designate proper names for certain biological products that include four-digit distinguishing suffixes. This 351(a) application is within the scope of this guidance. However, the issuing of the guidance occurred at a point in our review of the

application that did not allow for sufficient time for FDA to designate a proper name with a suffix, as described in the guidance. Therefore, in order to avoid delaying the approval of the application and in the interest of public health, we will approve the proper name as designated without a suffix [and intend to work with the applicant post-approval to implement a proper name consistent with the principles outlined in the guidance].

4 CONCLUSION & RECOMMENDATIONS

We find the Human Factors validation study results acceptable. Our review of the proposed container labels and carton labeling identified areas for improvement. We provide recommendations for Janssen Biotech in Section 4.1.

4.1 RECOMMENDATIONS FOR JANSSEN BIOTECH, INC.

A. General Comments

FDA issued a final guidance entitled *Nonproprietary Naming of Biological Products* on January 13, 2017 stating the Agency's intention to designate proper names for certain biological products that include distinguishing suffixes. This 351(a) application is within the scope of this guidance. However, the issuing of the guidance occurred at a point in our review of the application that did not allow for sufficient time for FDA to designate a proper name with a suffix, as described in the guidance. Therefore, in order to avoid delaying the approval of the application and in the interest of public health, we will approve the proper name as designated without a suffix, should your BLA be licensed, and intend to work with you post-approval to implement a proper name consistent with the principles outlined in the guidance. We would work with you to minimize the impact this would have to your manufacture and distribution of this product.

B. Container Labels (trade and sample)

1. Ensure there is adequate white space around the linear bar code to facilitate scanning.

C. Container Label (sample)

1. Consider removing the code [REDACTED] (b) (4) as it is non-sensical to healthcare providers and patients.

D. Container Label (trade)

1. Consider removing the code [REDACTED] (b) (4) as it is non-sensical to healthcare providers and patients.

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Tremfya that Janssen Biotech submitted on November 16, 2016.

Table 2. Relevant Product Information for Tremfya	
Initial Approval Date	N/A
Active Ingredient	Guselkumab
Indication	Treatment of adult patients 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 Week 0, Week 4 and every 8 weeks thereafter.
How Supplied	Carton of 1 PFS
Storage	Refrigerated at 2°C to 8°C (36°F to 46°F)
Container Closure	1 mL clear Type 1 glass syringe with a fixed 27-gauge ½" stainless steel needle

APPENDIX B. PREVIOUS DMEPA REVIEWS

B.1 Methods

On April 3, 2017 we searched the L:drive using the term, Tremfya and guselkumab, to identify reviews previously performed by DMEPA.

B.2 Results

Our search did not identify any relevant reviews related to the prefilled syringe presentation.

APPENDIX C. HUMAN FACTORS STUDY RESULTS

Summative Usability Study Report

Interface Analysis Associates

Oct. 2012

Objective:

The objective of this study was to validate the [REDACTED] ^{(b) (4)} for a broad user base, and to demonstrate that it can be correctly, safely and effectively used by patients, family caregivers and health care providers (HCPs) to deliver a subcutaneous injection across two different drug viscosities. The user population covered in this broad study included patients with Rheumatoid Arthritis (RA), Psoriasis or Crohn's disease, as well as family caregivers, and HCPs. The study was also used to determine whether any aspects of the syringe system or injection procedure led to patterns of confusion, failures, high-risk errors, or patient safety risks.

Study Design

Injection Naïve	Injection Experienced
Psoriasis and Crohn's Patients (N=15)	Rheumatoid Arthritis Patients (N=15)
Caregivers (N=15)	HCPs (N=15)
N=30	N=30
Total = 60 Participants	

Moderator Trained	Self-Trained
Psoriasis and Crohn's Patients (N=15)	Rheumatoid Arthritis Patients (N=15)
Caregivers (N=15)	HCPs (N=15)
N=30 (All Injection Naïve Participants)	N=30 (All Injection Experienced Participants)

Injection Naïve Group – 2 Sessions

Session 1		Session 2 (One Week Later)	
Trained by Moderator (acting as HCP)	Injection #1 – Supervised Injection by Trainer (Moderator)	Injection #2 – Unaided Injection	Injection #3 – Unaided Injection Opposite Viscosity
Context: Doctor's Office		Context: Home	

Injection Experienced Group – Single Session

Session 1			
Self-Train (Read IFU)	Injection #1 – Unaided Injection	Injection #2 – Unaided Injection	Injection #3 – Unaided Injection Opposite Viscosity
Contexts: Home (RA Patient) or Hospital (HCP)			

User Type	Training Condition
Injection Naïve	Trained By Moderator (acting as HCP)
Injection Experienced	Self-Trained by Reading IFU

User Group	Injection #1 (1 st Assigned Viscosity)	Injection #2 (1 st Assigned Viscosity)	Injection #3 (2 nd Assigned Viscosity)
Injection Naïve	30 Supervised Injections	30 Unaided Injections	30 Unaided Injections
Injection Experienced	30 Unaided Injections	30 Unaided Injections	30 Unaided Injections
TOTAL	180 Injections (30 Supervised, 150 Unaided)		

Drug Viscosity & Injection Site Manipulations

Participants were randomly assigned to one viscosity (2cP or 8cP) for their first and second injection trials. For the third injection, participants performed an injection with the opposite viscosity (high or low depending on their initial assigned viscosity). After administering the third injection, participants were asked if they noticed whether the injection was easier or harder and if the difference was significant or not. This manipulation assessed the suitability of the platform device over a range of expected drug viscosities.

Patients were also randomly assigned an injection site of either the abdomen or thigh while caregivers and HCPs were assigned to use the back of the arm. See the site assignment in the condition log in Appendix C.

SE comment:

Agree with study design.

Use Related Risk Analysis

Task	Risk*	Study technique	Range of Acceptable Performance	Performance	Observed Behaviors	Subjective Response
Knowledge of device wait time	Low	Participants were asked to state how long to wait before injecting for the device to warm to room temperature.	Must answer 30 minutes.	--	--	Participant verbal response.
Identification of injection site	Medium	Participants were asked to state the allowable injection site before any pad is applied to their body.	Must respond abdomen or thigh or back of arm.	--	--	Participant verbal response.
Open Packaging and Remove	Medium	Participants were observed	Must remove syringe without any damage.	Success removing syringe from	--	Subjective commentary on opening

Task	Risk*	Study technique	Range of Acceptable Performance	Performance	Observed Behaviors	Subjective Response
Syringe		regarding removal of the syringe from its packaging.		package.		and removing syringe from packaging.
Clean Injection Site Comprehension	Medium	Participants were asked to comprehend the section in the IFU related to cleaning the injection site	Must know to clean site during trial.	N/A	--	Subjective commentary on comprehending section in IFU related to cleaning injection site.
Remove Needle Cap	Medium	Participants were observed regarding removal of the cap.	Must remove cap without injury.	Success in removing cap.	Bends needle. Needle prick.	Subjective commentary on removing cap.
Pinch Skin Comprehension	Medium	Participants were asked to comprehend the section in the IFU related to pinching the skin.	Must know to pinch skin during trial.	N/A	--	Subjective commentary on comprehending section in IFU related to pinching skin.
Administer Full Dose	Medium	Participants were observed regarding their ability to administer the full injection.	Must depress plunger to administer full dose.	Success administering full dose.	Delivers partial dose.	Subjective commentary on starting injection.
Activates Needle Shield	Medium	Participants were observed regarding their ability to activate the needle shield at the site or near the site of the injection	Must activate the needle shield immediately after withdrawal of needle from site or proximal to injection site.	Success activating the needle shield	Location activated (on injection site or off injection site).	Subjective commentary on activating the needle shield.
Device Disposal Comprehension	High	Participants were asked to comprehend	Must know to dispose into sharps	N/A	--	Subjective commentary on

Task	Risk*	Study technique	Range of Acceptable Performance	Performance	Observed Behaviors	Subjective Response
		the section in the IFU related to device disposal.	container. Must know to dispose during trial.			comprehending section in IFU related to syringe disposal.

*Severity rating based on uFMEA (GBSC-TD-RPT-0099), Hazard analysis (GBSC-TD-RPT-0074)

Overview of Unexpected User Tasks/Actions (Unanticipated Risks)

There are always tasks that users should not perform or attempt, but that can be anticipated via the risk analysis. These are listed below.

Task	Risk	Study technique
Pre injection tampering (resulting in needle stick injuries or loss of drug)	Medium	Participants will be observed for any tampering or interaction with the device.
Needle stick	High	Participants will be observed for any needle stick injuries or close calls during the entire session.
Recaps needle	Medium	Participants will be observed for any instances of recapping the needle with the cap after administering the injection, which result in a needle stick.
Post injection tampering (resulting in needle stick injuries)	High	Participants will be observed for any tampering or interaction with the device.

Participant Demographics:

Factor	Criteria Applied	Participant Demographic Summary
Factors Applicable to All Participants (N=60)		
Age (RV & E)	A mix of ages was desired. Excluded if under 18 years of age.	Ranged from 18 to 71 years Mean Age: 40.58 Years Median Age 40.0 years Standard Deviation: 13.25 years
Gender (RV)	A mix of gender was desired.	Males: 16/60 (27%) Females: 44/60 (73%)
Occupation (RV)	A mix of occupations was desired.	Medical (Advice Nurse, LVN, Medical Assistant, RN) – (x15) Sales – (x5) Accounting Activities Director Attorney Audiology Tech Choreographer Consultant Councilor Day Care Director Of National Accounts Disability Drafter

		<p>Education</p> <p>Executive Assistant</p> <p>Food Service</p> <p>Graphic Design</p> <p>Homemaker</p> <p>Insurance Agent</p> <p>Interior Designer</p> <p>Legal Writer</p> <p>Lighting Designer</p> <p>Manager</p> <p>Retired</p> <p>Naturalist</p> <p>Production Sign Manager</p> <p>Retired</p> <p>Social Worker</p> <p>Special Education</p> <p>Student</p> <p>Teacher</p> <p>Transitional Housing</p> <p>Travel Agent</p> <p>Unemployed</p> <p>Writer, Photographer</p>
Education (RV)	<p>All participants were screened for their highest level of completed education.</p> <p>Desired was a mix of different education levels.</p>	<p>11th Grade: 2/60 (3%)</p> <p>High School Diploma: 20/60 (33%)</p> <p>Associates: 4/60 (7%)</p> <p>Trade School: 1/60 (2%)</p> <p>Nursing School: 15/60 (25%)</p> <p>Bachelor's Degree: 14/60 (23%)</p> <p>Master's Degree: 3/60 (5%)</p> <p>Doctorate: 1/60 (2%)</p>
Ethnicity (RV)	<p>All participants were screened for their ethnicity.</p> <p>Desired to include a mix of different ethnicities.</p>	<p>African American: 3/60 (5%)</p> <p>Asian: 10/60 (17%)</p> <p>Caucasian: 32/60 (53%)</p> <p>Hispanic: 8/60 (13%)</p> <p>Indian: 1/60 (2%)</p>

		Mixed: 1/60 (2%) Pacific Islander: 5/60 (8%)
Factors Applicable to all Patient Participants (N=30)		
What medical condition do you have? (RV & E)	All patients were screened for what medical condition they had. Patients were excluded if they did not have Crohn's, Psoriasis, or RA.	Crohn's: 7/30 (23%) Psoriasis: 8/30 (27%) RA: 15/30 (50%)
When were you medically diagnosed with your condition? (FYI)	All patients were screened for when they were diagnosed with their medical condition.	Less than 1 year: 1/30 (3%) 1 to 5 years: 9/30 (30%) 6 to 10 years: 8/30 (27%) 10+ years: 12/30 (40%)
Are you currently taking medication for your condition? (FYI)	All patients were screened for whether or not they took a medication for Crohn's, Psoriasis, or RA.	Yes: 29/30 (97%) No: 1/30 (3%)
What medications are you currently taking for your condition? (FYI)	All patients were screened for what medications they were taking to treat their Crohn's, Psoriasis, or RA.	6MP: 1/29 Aleve: 1/29 Balsalazide: 1/29 Benty: 1/29 Betamethasone: 3/29 Celebrex: 1/29 Clobetasol Propionate: 1/29 Codeine: 1/29 Dovonex: 2/29 Enbrel: 4/29 Humira: 2/29 Hydrocortisone: 1/29 Ibuprofen: 1/29 Indomethacin: 1/29 Kineret: 1/29 Light box therapy: 2/29 Mercaptopurine: 1/29 Methotrexate: 6/29

		<p>Metrogel: 1/29 Norco: 1/29 Photo Therapy: 2/29 Prednisone: 3/29 Remicade: 1/29 Soriatane: 1/29 Triamcinolone Acetonide: 2/29 Urea Cream 40%: 1/29 Vectical: 2/29 Vicodin: 1/29 Vistaril: 1/29</p> <p>Note: Some participants stated multiple medications.</p>
<p>Do you have experience self-administering an injection? (RV)</p>	<p>All patients were screened for whether or not they had an experience self-administering an injection.</p> <p>Desired to include 15 Crohn's and Psoriasis patients with no injection experience and 15 RA patients with injection experience.</p>	<p>Yes: 15/30 (50%) No: 15/30 (50%)</p>
<p>Do you have any arthritis pain, stiffness or weakness in your hands or fingers? (RV)</p>	<p>All patients were screened as to whether or not they have any stiffness or weakness in their hands or fingers.</p> <p>Desired to include some RA patients who have weakness or stiffness in their hands or fingers.</p>	<p>Yes: 16/30 (53%) No: 14/30 (47%)</p>
<p>Factors Applicable to all RA Patient Participants (N=15)</p>		
<p>Where on your body does your condition affect you? (FYI)</p>	<p>All RA participants were screened for where on their body their RA affects them.</p>	<p>Hands: 8/15 Knees: 7/15 Entire body: 4/15 Feet: 3/15</p>

		Hips: 3/15 Back: 2/15 Elbows: 2/15 Neck: 2/15 Shoulders: 1/15 Ankle: 1/15 Note: Some participants stated multiple areas.
Factors Applicable to all Caregiver Participants (N=15)		
Have you ever given yourself or someone else an injection of any kind? (E)	All caregiver participants were screened for whether or not they have given an injection of any kind. Excluded if had any prior injection experience.	No: 15/15 (100%)
Factors Applicable to all HCP Participants (N=15)		
Do you treat patients with Crohn's, Psoriasis or RA? (E)	All HCP's were screened for whether or not they treat patients with Crohn's, Psoriasis or RA. Excluded if they did not treat these types of patients.	Yes: 15/15 (100%)
How many years of experience do you have treating these patients? (FYI)	All HCP's were screened for how many years of experience they have treating patients with Crohn's, Psoriasis or RA.	0 – 5 years: 11/15 (73%) 6 – 10 years: 4/15 (27%)

Summary of the 90 Unaided Trials

The following table presents a summary of the task measures across all three injection trials organized by risk (highest to lowest).

Observation	Risk Level	Trial 1 – Unaided Injections (N=30)	Trial 2 - Unaided Injections (N=60)	Overall Results
Measures – High Risk				
Knowledge of Device Disposal (IFU Comprehension)	High	30/30 (100%)	60/60 (100%)	90/90 (100%)
Needle Stick (Observation)	High	0/30 (0%)	0/60 (0%)	0/90 (0%)
Pre or Post-Injection Tampering	High	0/30 (0%)	0/60 (0%)	0/90 (0%)
Measures – Medium Risk				
Knowledge of Injection Sites (IFU Comprehension)	Medium	30/30 (100%)	60/60 (100%)	90/90 (100%)
Identification of Expiration Date (Labeling Comprehension)	Medium	--	--	60/60 (100%)
Opening Package and Removing Syringe	Medium	30/30 (100%)	60/60 (100%)	90/90 (100%)
Clean Injection Site Comprehension (IFU Comprehension)	Medium	--	--	60/60 (100%)
Needle Cap Removal (Observation)	Medium	30/30 (100%)	60/60 (100%)	90/90 (100%)
Pinch Skin Comprehension (IFU Comprehension)	Medium	--	--	60/60 (100%)
Administration of Full Dose (Observation)	Medium	30/30 (100%)	60/60 (100%)	90/90 (100%)
Activation of Needle Shield (Observation)	Medium	29/30 (97%)	59/60 (98%)	88/90 (98%)
Recaps Needle (Observation)	Medium	0/30 (0%)	0/60 (0%)	0/90 (0%)
Measures – Low Risk				
Knowledge of Device Wait time (IFU Comprehension)	Low	30/30 (100%)	--	30/30 (100%)

Injection (Trial 1 - cP #1) Measures

Observation	Risk Level	Injection Naïve Psoriasis, Crohn's, Caregiver (N=30)	Injection Experienced RA, HCP (N=30)	Overall (N=60)
Knowledge Probes				
Knowledge of Device Wait Time	Low	30/30 (100%)	30/30 (100%)	60/60 (100%)
Knowledge of Acceptable Injection Sites	Medium	30/30 (100%)	30/30 (100%)	60/60 (100%)
Knowledge of Ancillary Supplies	Medium	30/30 (100%)	30/30 (100%)	60/60 (100%)
Packaging				
Opens Package and Removes Syringe	Medium	30/30 (100%)	30/30 (100%)	60/60 (100%)
Injection Preparation				
Checks Drug Window	Medium	30/30 (100%)	30/30 (100%)	60/60 (100%)
Cleans Injection Site	Medium	30/30 (100%)	30/30 (100%)	60/60 (100%)
Removes Needle Cover	Medium	30/30 (100%)	30/30 (100%)	60/60 (100%)
Injection				
Pinches Skin	Medium	30/30 (100%)	26/30 (87%)	56/60 (93%)
Failure to insert needle at correct angle (15-90 degrees)	Medium	0/30 (0%)	0/30 (0%)	0/60 (0%)
Fully Depresses Plunger	Medium	30/30 (100%)	30/30 (100%)	60/60 (100%)
Failure to Activate Safety Mechanism	Medium	0/30 (0%)	1/30 (3%)	1/60 (2%)*
Activates Needle Shield	Medium			
<i>Near Site</i>		30/30 (100%)	26/29 (90%)	56/59 (95%)*
<i>Off Site</i>		--	3/29 (10%)	3/59 (5%)
Post Injection				
Failure to Dispose Syringe in Sharps Container	High	0/30 (0%)	0/30 (0%)	0/60 (0%)
Unanticipated Events				
Tampers With Device or Packaging and Injures Self or Damages Product?	Medium	0/30 (0%)	0/30 (0%)	0/60 (0%)
Needle Prick	High	0/30 (0%)	0/30 (0%)	0/60 (0%)

Observation	Risk Level	Injection Naïve Psoriasis, Crohn's, Caregiver (N=30)	Injection Experienced RA, HCP (N=30)	Overall (N=60)
Recaps Needle	Medium	0/30 (0%)	0/30 (0%)	0/60 (0%)

*Note - One participant (P15 - RA) did not activate the safety mechanism although the plunger had been fully depressed and no medication was left in the syringe.

During trial 1, there was one injection experienced participant (P15 - severe RA) who fully delivered the dose, but did not activate the safety mechanism. The participant took the syringe and immediately disposed of it after the safety mechanism did not activate. Post session inspection of the syringes showed that the participant had delivered the full dose but simply did not complete the final press in order to activate the safety mechanism. This could have been due to the participants severe RA in her hands, coupled with the high cP of her first injection. The participants' unfamiliarity with the device and the high cP seemed to make it harder to distinguish that more pressure was needed at the end of the plunger travel to activate the safety mechanism.

Unaided Injection (Trial 2 - cP #1) Measures

Observation	Risk Level	Injection Naïve Psoriasis, Crohn's, Caregiver (N=30)	Injection Experienced RA, HCP (N=30)	Overall (N=60)
Packaging				
Opens Package and Removes Syringe	Medium	30/30 (100%)	30/30 (100%)	60/60 (100%)
Injection Preparation				
Checks Drug Window	Medium	30/30 (100%)	30/30 (100%)	60/60 (100%)
Cleans Injection Site	Medium	30/30 (100%)	30/30 (100%)	60/60 (100%)
Removes Needle Cover	Medium	30/30 (100%)	30/30 (100%)	60/60 (100%)
Injection				
Pinches Skin	Medium	28/30 (93%)	26/30 (87%)	54/60 (90%)
Failure to insert needle at correct angle (15-90 degrees)	Medium	0/30 (0%)	0/30 (0%)	0/60 (0%)
Fully Depresses Plunger	Medium	30/30 (100%)	30/30 (100%)	60/60 (100%)
Failure to Activate Safety Mechanism	Medium	0/30 (0%)	1/30 (3%)	1/60 (2%)*
Activates Needle Shield	Medium			
<i>Near Site</i>		28/29 (97%)*	26/30 (87%)	54/59 (92%)*
<i>Off Site</i>		1/29 (3%)*	4/30 (10%)	5/59 (8%)*
Post Injection				
Failure to Dispose Syringe in Sharps Container	High	0/30 (0%)**	0/30 (0%)	0/60 (0%)
Unanticipated Events				
Tampers With Device or Packaging and Injures Self or Damages Product?	Medium	0/30 (0%)	0/30 (0%)	0/60 (0%)
Needle Prick	High	0/30 (0%)	0/30 (0%)	0/60 (0%)
Recaps Needle	Medium	0/30 (0%)	0/30 (0%)	0/60 (0%)

*Note - One participant (P19 - Psoriasis) did not activate the safety mechanism although the plunger had been fully depressed and no medication was left in the syringe. The participant's unique hand posture (plunger pad resting against pad of hand), orientation of the injection pad in conjunction with the high cP syringe could have led to this error.

**Note - One participant (P27 - Crohn's) inadvertently placed the covered syringe into the regular garbage. When asked how the process went the participant realized the mistake of throwing the syringe in the garbage and put it into the sharps container. The participant understood the need to dispose the syringe in the sharps but forgot due to an artifact of the study.

During trial 2, there was one injection naive participant (P19 - Psoriasis) who fully delivered the dose, but did not activate the safety mechanism. The participant took the syringe and immediately disposed of it after the safety mechanism did not activate. Post session inspection of the syringe showed that the participant had delivered the full dose but simply did not complete the final press in order to activate the safety mechanism. The participant stated that she thought that she had pressed down all the way but admitted she did not hear a click at the end of the injection, but felt resistance. The participant was using a unique hand posture and the plunger head seemed to be stopped by the palm of her hand on a few occasions. In addition, the participants' finger was overlapping the plunger head by a lot and may have come in contact with the activation tabs during the injection.

All of the participants (60/60, 100%) remembered to check the drug window to evaluate the drug quality. All of the participants went on to remove the needle cap successfully and insert the syringe at the correct angle (15-90 degrees). Some of the participants in the injection experienced group (4/30, 13%) and some in the injection naïve group (2/30, 7%) did not pinch their site during the injection.

3.4 TRIAL 3 - (UNAIDED INJECTION - CP #2) RESULTS

The third injection of the study was included to test the acceptability of different syringe viscosities in order to assess if users experienced significant force differences (between a 2cP and 8cP syringe) and whether the 8cP syringe represented an acceptable force for the patient population. Participants were given a syringe with the opposite cP value than what they experienced during their first two injection trials. The order was counterbalanced so that half of the participants received two low viscosity syringes and then a high viscosity syringe, and half of the participants received two high viscosity syringes and then a low viscosity syringe.



Participants Performing their third injection with the opposite viscosity syringe

Trial 3 (Unaided Syringe Force Acceptability) Injection Findings

The results of the third trial indicate that all of the participants (60/60, 100%) would accept the higher viscosity syringe (8cP) as an injection they would perform on a weekly basis. Participants that experienced the high cP syringe first (29/29, 100%) found the lower cP syringe (2cP) to be acceptable, while the participants that experienced the low cP first (31/31, 100%) also felt that the increase to the high cP syringe was still acceptable.

Root Cause Analysis for Use Error Failure to Activate Safety Mechanism

Task Error - Failure to activate the safety mechanism (N=1)

Participant Type	Injection Condition	Task Failure Type	General Description of Error	Safety Risk Level	Dosing Risk Level
P15 (RA)	High (8cP) - Injection Trial 1	Failure to activate the safety mechanism.	After fully depressing the syringe and delivering the full dose, the patient did not continue to press down until the safety mechanism activated	Medium	None
<p>Q to Patient: Why do you think this error occurred? Answer: I think I pressed it, but the thing didn't come down. I don't know.</p>					
<p>Q to Patient: What would you change about the packaging, syringe system design, syringe system labeling or instructions to prevent this error? Answer: I didn't hear a click. I thought it was all the way down because I felt it stop. Maybe if you could know that there was or wasn't going to be a click that would help.</p>					
<p>IAA Commentary/Mitigation Response: During the first trial the participant was having difficulty finding the best orientation of the syringe with her severe RA. The participant was able to fully depress the plunger for the dose, but the combination of the high cP and her severe RA made the injection slow and steady. The speed with which she plunged may have led to her feeling that once the plunger had made contact with the plastic activation tabs that the device was complete. Coupled with the lack of the click (commonly associated with higher speed and more forceful movements of the plunger) the participant felt that she was done when she removed the needle from the skin pad. She immediately disposed of the syringe in the sharps container. When examined by the moderator the medication was completely expelled and activation of the safety mechanism took place with a very slight push of the plunger. This participant was successful on her other trial with the same syringe and drug viscosity.</p>					

Participant Type	Injection Condition	Task Failure Type	General Description of Error	Safety Risk Level	Dosing Risk Level
 <p>The image consists of two photographs stacked vertically. Both photographs show a person wearing a pink long-sleeved shirt and a watch on their left wrist. They are performing a procedure involving a syringe and a yellow container. In the top photograph, the person is holding a syringe with their left hand and the yellow container with their right hand. The syringe is inserted into the container. In the bottom photograph, the person is holding the syringe with their left hand and the yellow container with their right hand. The syringe is inserted into the container. The background is a dark surface, possibly a table or desk.</p>					

Participant Type	Injection Condition	Task Failure Type	General Description of Error	Safety Risk Level	Dosing Risk Level
   <p>The combination of the participants' severe RA and the slow injection speed required by her hand impairment made it more difficult for her to ascertain if she</p>					

Participant Type	Injection Condition	Task Failure Type	General Description of Error	Safety Risk Level	Dosing Risk Level
<p>had completed the plunger movement necessary for needle guard activation. This could be an issue with a small percentage of participants with severe hand degradation while using the higher cP medication. However, the overwhelming majority of participants had no issues depressing or activating the safety mechanism on the 8cP syringes, even with RA.</p>					

Task Error - Failure to activate the safety mechanism (N=1)

Participant Type	Injection Condition	Task Failure Type	General Description of Error	Safety Risk Level	Dosing Risk Level
P19 (Psoriasis)	High (8cP) - Injection Trial 2	Failure to activate the safety mechanism.	After fully depressing the syringe and delivering the full dose, did not continue to press until the safety mechanism activated.	Medium	None
<p>Q to Patient: Why do you think this error occurred? Answer: Not sure. I thought I pushed down all the way.</p>					
<p>Q to Patient: What would you change about the packaging, syringe system design, syringe system labeling or instructions to prevent this error? Answer: I would mention to push down until you hear a click in the instructions.</p>					
<p>IAA Commentary/Mitigation Response: A combination of the participants' unique hand posture (with palm of hand resting on the injection pad, partially interfering with the plunger movement), thumb overlapping the plunger pad, the orientation of the injection skin pad, and the higher viscosity drug made detecting the stop of the plunger more difficult for this participant. After the mechanism did not activate the participant immediately threw the syringe into the sharps container. The participant had performed the previous injection successfully without any indices of confusion or frustration. The moderator evaluated the syringe after the session and determined that the full dose had been delivered and that the plunger head was resting on the plastic safety mechanism activation tabs. A very slight push caused the safety to activate. The fact that the participant successfully delivered the full dose meant that there was no dosing risk level.</p>					

Participant Type	Injection Condition	Task Failure Type	General Description of Error	Safety Risk Level	Dosing Risk Level
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Participant Type	Injection Condition	Task Failure Type	General Description of Error	Safety Risk Level	Dosing Risk Level
					
<p>We feel this error does not require mitigation, save for perhaps calling out the click sound more explicitly in the IFU. The participant performed the previous high cP injection successfully and delivered the full dose during injection session 2. The participant also knew to dispose of the syringe immediately in case of a failure of the safety mechanism. Based on the participant responses and previous successful performance this error does not represent a clear pattern of preventable failures or errors.</p>					

Conclusion

The (b) (4) delivery system (b) (4), package labeling and associated instructions for use performed extremely well on all aspects of user interaction and knowledge of the process.

We observed 100% of participants administer their full dose, with only a few medium risk level errors (failure to activate safety mechanism after complete delivery of dose). There were no patterns of behavior or errors during the study and both of the errors that were committed were mitigated by the fact that the participants immediately disposed of the syringe in a sharps container (which is the optimal method in case of device safety mechanism failure). Based on the data from the study we can conclude the following about the safety and effectiveness of the (b) (4) delivery system (b) (4):

- The study revealed no patterns of preventable failures, errors, or user difficulties associated with any high, medium or low risk tasks by the intended user populations (RA, Psoriasis, Crohn's, HCP's and family caregivers) under all use cases and contexts.

Based on the results of the study we conclude that the (b) (4) delivery system (b) (4) can be correctly, safely and effectively used by the intended user audiences.

IFU Tested in HF Study:

Instructions for Use

Prefilled Syringe | Instructions for Use

Read all instructions below before using the prefilled syringe.
 XYZ is a prefilled syringe with the exact dose you need. The syringe is a single, one-time use device and includes a needle guard that automatically covers the needle after complete delivery of the medication.

Questions? For injection assistance, please call your doctor or the XYZ help line at XXX-XXX-XXXX.

Step 1 - Gather and Inspect the Supplies for your Injection

- Remove the carton from the refrigerator. Check the expiration date on the back of the carton. **DO NOT** use if expired.
- Remove a prefilled syringe from the carton by grasping the middle of the syringe body.
- Allow the prefilled syringe to sit at room temperature for 30 minutes to naturally warm to room temperature.
- Hold the syringe by the body and look at the medication through the inspection window. Make sure the liquid is clear and colorless to slightly yellow in color. You may also notice an air bubble. This is normal.
- Find a well-fit, clean surface and place the following supplies within reach:
 - The prefilled syringe
 - alcohol swab
 - cotton ball or gauze pad
 - sharps container for syringe disposal

Wait 30 Minutes

Step 2 - Choose and Prepare the Injection Site

- The recommended injection site is the top of your middle thighs. You can also use the lower part of the abdomen below or to the side of the navel/belly button, except for the two-inch area directly around the navel. If a caregiver is giving you the injection, the outer area of the upper arm may also be used.
- Wipe the injection site with an alcohol swab.
- Allow the skin to dry before injecting.
- Rotate your injection site with each injection.

Step 3 - Inject Medication with the Prefilled Syringe

- Hold the body of the prefilled syringe with one hand (with the needle facing away from you), and pull the needle cover straight off extending your hand away from the needle.
- Hold the body of the prefilled syringe in one hand between the thumb and index finger. Use your other hand to gently pinch the skin that you previously cleaned. Hold firm. Use a quick, dart-like motion to insert the needle into the pinched skin at about a 45-degree angle.
- Use your thumb to push the plunger until the plunger head is completely between the needle guard activation clips. This will assure that you have received the full dose. When the plunger is pushed as far as it will go, keep pressure on the plunger head.

Step 4 - Remove the Needle and Activate the Safety Guard

- Take the needle out of the skin.
- Slowly take your thumb off of the plunger head. This will let the empty syringe move up until the entire needle is covered by the needle guard.
- DO NOT** point the needle at yourself or anyone else.

Step 5 - Dispose the Used Syringe

- Place the used prefilled syringe into a closable, puncture-resistant container right away.
- After the injection there may be a small amount of blood or liquid at the injection site, which is normal. You can press a cotton ball or gauze over the injection site for 10 seconds. You may cover the injection site with a small adhesive bandage, if needed.

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APPENDIX D. ISMP NEWSLETTERS

N/A

APPENDIX E. FDA ADVERSE EVENT REPORTING SYSTEM (FAERS)

N/A

APPENDIX F. OTHER

N/A

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CARLOS M MENA-GRILLASCA
05/12/2017

SARAH K VEE
05/12/2017

QUYNHNHU T NGUYEN
05/15/2017

LUBNA A MERCHANT
05/15/2017

**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: April 21, 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)

Sharon Mills, BSN, RN, CCRP
Senior Patient Labeling
Division of Medical Policy Programs (DMPP)

From: Shawna Hutchins, MPH, BSN, RN
Senior Patient Labeling Reviewer
Division of Medical Policy Programs (DMPP)

Silvia Wanis, PharmD, CPH
Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

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

Drug Name (established name): TRADENAME (guselkumab)

Dosage Form and Route: injection, for subcutaneous use

Application Type/Number: BLA 761061

Applicant: Janssen Biotech, Inc.

1 INTRODUCTION

On November 16, 2016, Janssen Biotech, Inc., submitted for the Agency's review an original Biologics Licensing Application (BLA) 761061 for TRADENAME (guselkumab) injection, to support the approval of TRADENAME (guselkumab) injection for subcutaneous use, for the treatment of adults with moderate-to-severe plaque psoriasis who are candidates for systemic 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 November 18, 2016, for DMPP and OPDP to review the Applicant's proposed Medication Guide (MG) and Instructions for Use (IFU) for TRADENAME (guselkumab) injection, for subcutaneous use.

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

2 MATERIAL REVIEWED

- Draft TRADENAME (guselkumab) MG and IFU received on November 16, 2016, and received by DMPP and OPDP on April 7, 2017.
- Draft TRADENAME (guselkumab) Prescribing Information (PI) received on November 16, 2016, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on April 7, 2017.
- Approved SILIQ (brodalumab) comparator labeling dated February 2, 2017.
- Approved TALTZ (ixekizumab) reference labeling dated March 22, 2016.

3 REVIEW METHODS

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

In our collaborative review of the MG and IFU we:

- simplified wording and clarified concepts where possible
- ensured that the MG and IFU are consistent with the Prescribing Information (PI)

- removed unnecessary or redundant information
- ensured that the MG and IFU are free of promotional language or suggested revisions to ensure that it is free of promotional language
- ensured that the MG meets the Regulations as specified in 21 CFR 208.20
- ensured that the MG and IFU meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)
- ensured that the MG and IFU are consistent with the approved comparator labeling where applicable.

4 CONCLUSIONS

The MG and IFU are acceptable with our recommended changes.

5 RECOMMENDATIONS

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

Please let us know if you have any questions.

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SHAWNA L HUTCHINS
04/21/2017

SILVIA WANIS
04/21/2017

SHARON R MILLS
04/21/2017

LASHAWN M GRIFFITHS
04/21/2017

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

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

Memorandum

Date: April 19, 2017

To: Matthew White, RPM
Regulatory Project Manager
Division of Dermatology and Dental Products (DDDP)

From: Silvia Wanis, PharmD, CPH
Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

Subject: **BLA 761061**
OPDP labeling comments for TRADENAME (guselkumab)
injection, for subcutaneous use

Reference is made to DDDP's November 18, 2016 consult request for OPDP's comments regarding the proposed labeling for TRADENAME (guselkumab) injection.

OPDP's comments on the proposed labeling, which are based on the draft version of the Package Insert (PI) and the Carton/Container labeling emailed by Matthew White on April 7, 2017, are provided below.

OPDP's review and comments on the proposed Medication Guide and IFU was conducted jointly with the Division of Medical Policy Programs (DMPP). This review will be submitted under separate cover at a later date.

If you have any questions, please feel free to contact me:

Silvia Wanis: 301-796-5198; silvia.wanis@fda.hhs.gov

Thank you! OPDP appreciates the opportunity to provide comments on these materials.

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SILVIA WANIS
04/21/2017

**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: 2016-02-11**

Date: April 13, 2017

Reviewer / Acting TL: Kira Leishear White, PhD, MS
Division of Epidemiology I

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

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

Drug Name(s): Guselkumab

Application Type/Number: BLA 761061

Applicant/sponsor: Janssen Biotech, Inc.

OSE RCM #: 2017-303

EXECUTIVE SUMMARY (place “X” in appropriate boxes)

Memo type

-Initial	X	
-Interim		
-Final		
Source of safety concern		
-Peri-approval	X	
-Post-approval		
Is ARIA sufficient to help characterize the safety concern?		
Safety outcome:	Short-term Lymphoma	Long-term Malignancy
-Yes	X	
-No		X
If “No”, please identify the area(s) of concern.		
-Surveillance or Study Population		
-Exposure		
-Outcome(s) of Interest		X
-Covariate(s) of Interest		X
-Surveillance Design/Analytic Tools		

1. BACKGROUND INFORMATION

1.1. Medical Product

Guselkumab is a recombinant human immunoglobulin G1 lambda (IgG1λ) monoclonal antibody and is an interleukin-23 (IL-23) antagonist. IL-23 stimulates Th17 cell differentiation and survival and regulates IL-17A, a central pro-inflammatory effector cytokine implicated in the pathogenesis of psoriasis. Guselkumab inhibits IL-23 signaling by binding to the p19 subunit of IL-23.

The proposed indication is for the treatment of adults with moderate-to-severe plaque psoriasis who are candidates for systemic therapy or phototherapy.

This memo reflects the discussions, recommendations, and determinations between the Division of Epidemiology I (DEPI-I), the Division of Dermatology and Dental Products (DDDP), and Dr. Michael Nguyen during the Signal Assessment Meeting (SAM), held on March 15, 2017.

1.2. Describe the Safety Concern

A theoretical risk of malignancy exists, due to immunosuppressive effects, and is hypothesized to be a potential risk for all psoriasis biologics. Cosentyx (secukinumab), Taltz (ixekizumab), and Siliq (brodalumab) each were issued FDA post-marketing requirements (PMRs) to conduct a prospective, observational study to assess the theoretical risk of long-term malignancy, with a minimum follow-up length of 8 years. In the Phase 3 Clinical Trials for guselkumab, through week 48 of treatment, there were 6 cases of non-melanoma skin cancer, 2 cases of prostate cancer, and 1 case of breast cancer, out of 823 subjects. In the placebo arm, there were 0 cases of malignancy out of 422 subjects; however, subjects were only followed for 16 weeks. 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. DDDP hypothesized that the risk of lymphoma could be related to exposure with guselkumab.

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

Purpose (place an “X” in the appropriate boxes; more than one may be chosen)

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 conditions for a PMR under FDAAA are satisfied, as the purpose is to identify an unexpected serious risk when available data indicate the potential for a serious risk. In adults with psoriasis, treated with guselkumab, the available data indicate the potential for serious risk of malignancy, possibly delayed, and a need for a post-market study for malignancy. The available data consists of guselkumab’s mechanism of action as an immunosuppressive, as this is a theoretical concern with all psoriasis biologics.

In Section 2 of this ARIA Sufficiency Memo, the FDA considers whether ARIA is sufficient to be used in the post-marketing setting to assess the risk of malignancy after guselkumab exposure.

1.5. Effect Size of Interest or Estimated Sample Size Desired

The regulatory goal for evaluating the risk of malignancy in ARIA is for signal detection (i.e., post-marketing surveillance), rather than a hypothesis-driven study. Therefore, *a priori* levels of risk to rule in or out for the risk of malignancy, versus other psoriasis treatments, have not been determined as they would be for a protocol-based assessment.

2. SURVEILLANCE OR DESIRED STUDY POPULATION

2.1. Population

The study population will consist of a general population of adults (≥18 years of age) exposed to guselkumab. DDDP identified the study population to be the patient population of guselkumab-users, restricted to the proposed indication (i.e., adults with psoriasis). The comparator populations will be 1) adults with psoriasis exposed to other psoriasis biologic medications and 2) adults with psoriasis exposed to non-biologic systemic medications.

2.2. Is ARIA sufficient to assess the intended population?

We anticipate that guselkumab users with diagnosis codes for psoriasis [ICD10 code: L40] will be identified in the Sentinel database. Identifying a comparable patient population using other psoriasis systemic therapies will be possible in Sentinel. Comparator populations will include adults with psoriasis diagnosis codes using other biologic therapies indicated for psoriasis as well as non-biologic systemic medications indicated for psoriasis. While the Sponsor is only seeking an indication for psoriasis for guselkumab at this time, many other biologics and non-biologic systemic medications indicated for psoriasis are also indicated for other diseases. Restricting both the guselkumab patient population as well as the comparator populations to patients with diagnosis codes for psoriasis will help ensure the cohorts are comparable.

We deem Sentinel sufficient to identify patients with psoriasis, using ICD-10 diagnosis codes [L40] exposed to guselkumab or comparator treatments. 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.¹ 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.² 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. EXPOSURES

3.1. Treatment Exposure(s)

Patients who received at least one prescription for guselkumab can be identified in health care claims data, in inpatient and outpatient settings, using coded information.

3.2. Comparator Exposure(s)

Two comparator populations were identified during the SAM, by DEPI-I and DDDP. One comparator population would be other psoriasis biologic medications, and another comparator population would be non-biologic systemic medications. Health care claims data can be used to identify these comparator exposures as well, in both inpatient and outpatient settings, using coded information.

3.3. Is ARIA sufficient to identify the exposure of interest?

ARIA allows for the identification of dispensings of both inpatient and outpatient prescriptions. Although, coded data on any injections administered during hospitalization may not be available. Guselkumab is packaged as a single-use pre-filled syringe which may be self-administered or given by a caregiver or clinician. This is consistent with many other psoriasis biologic medications on the market (e.g., Cosentyx, Taltz, Stelara, Enbrel). ARIA only provides coded information on dispensings and does not include information on whether the medications were actually administered. We anticipate any bias associated with adherence to be non-differential misclassification, which we expect to be low. Since biologic medications are expensive and relief from psoriasis is desired and needed, we believe most patients will adhere to the treatment. We also believe that ARIA will capture these dispensings since most will be outpatient prescriptions. Thus, we consider ARIA to be sufficient for capturing exposure to guselkumab and comparator treatments.

¹ Lofvendahl S, Theander E, Svensson A, Carlsson KS, Englund M, Petersson IF. Validity of diagnostic codes and prevalence of physician-diagnosed psoriasis and psoriatic arthritis in southern Sweden – a population-based register study. *PLoS One*. 2014; 9: e98024.

² Asgari MM, Wu JJ, Gelfand JM, et al. Validity of diagnostic codes and prevalence of psoriasis and psoriatic arthritis in a managed care population, 1996-2009. *Pharmacoepidemiol Drug Saf*. 2013; 22(8): 842-849.

4. OUTCOME(S)

4.1. Outcomes of Interest

The outcome of interest is malignancy, which will be assessed based on diagnosis codes, possibly in combination with procedure codes. DDDP was also specifically interested in assessing the risk of lymphomas, which may have a shorter latency compared to other malignancies. DDDP hypothesized that the risk of lymphoma could be related to exposure with guselkumab.

4.2. Is ARIA sufficient to assess the outcome of interest?

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.³ 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.⁴ 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.⁵ 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.

One limitation in using ARIA to assess malignancy is that clinical characteristics of malignancy which may be of interest are not available in claims data. Diagnostic or procedure codes cannot provide detailed narratives describing the clinical details of the malignancy. However, the main limitation in using ARIA to assess malignancy is the short length of follow-up available in Sentinel. Roughly 75% of patients in the Sentinel database have at most 3 years of follow-up data available [See Figure 1 below]. Assessing long-latency outcomes using ARIA, such as long-latency malignancies would not be sufficient in ARIA. In the future, length of enrollment in the Sentinel database may change, but the current data are not promising at this time for future analyses. Other psoriasis biologic medications have post-marketing studies with a minimum of 8 years of follow-up to assess malignancy. Also, another major limitation in assessing all malignancies is that the sensitivity and

³ Setoguchi S, Solomon D, Glynn R, Cook E, Levin R, Schneeweiss S. Agreement of diagnosis and its date for hematologic malignancies and solid tumors between medicare claims and cancer registry data. *Cancer Causes Control*. 2007;18(5):561-569.

⁴ 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.

⁵ Schumock GT, Lee TA, Pickard AS, et al. Mini-Sentinel Methods: Alternative methods for health outcomes of interest validation. August 31, 2013.
https://www.sentinelinitiative.org/sites/default/files/SurveillanceTools/ValidationsAndLiterature/Mini-Sentinel-Alternative-Methods-for-Health-Outcomes-of-Interest-Validation_0.pdf

PPV ranged greatly depending on the type of cancer in claims databases, 40-90% for sensitivity and 19-82% for PPV.³ So for certain malignancies with low sensitivity and PPV, outcome misclassification is more likely to be a major concern. Leukemia in particular had low sensitivity (ranging from 42% to 74%) and low PPV (ranging from 19% to 43%), depending on the definition used.

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. We are also interested in detecting large risks and consider potential outcome misclassification bias to be non-differential, thus we regard potential bias towards the null to be of less concern. Given that the validation studies of lymphoma mentioned above showed reasonably-well validation (i.e., sensitivity, specificity, and PPV), and that lymphoma can be assessed short-term in Sentinel (e.g., ~2-3 years of follow-up), we consider ARIA to be sufficient to assess short-term lymphoma.

Because of the limitation of insufficient long-term follow-up data for assessing the risk of long-latency malignancy as well as the variability of PPV among the numerous types of malignancy, we consider ARIA to not be sufficient to assess long-term malignancy (i.e., all types). As shown in Figure 1 below, roughly 4% of the Sentinel patient population would have at least 8 years of follow-up, as was required for PMR observational studies for other psoriasis biologics [see Section 1.2].

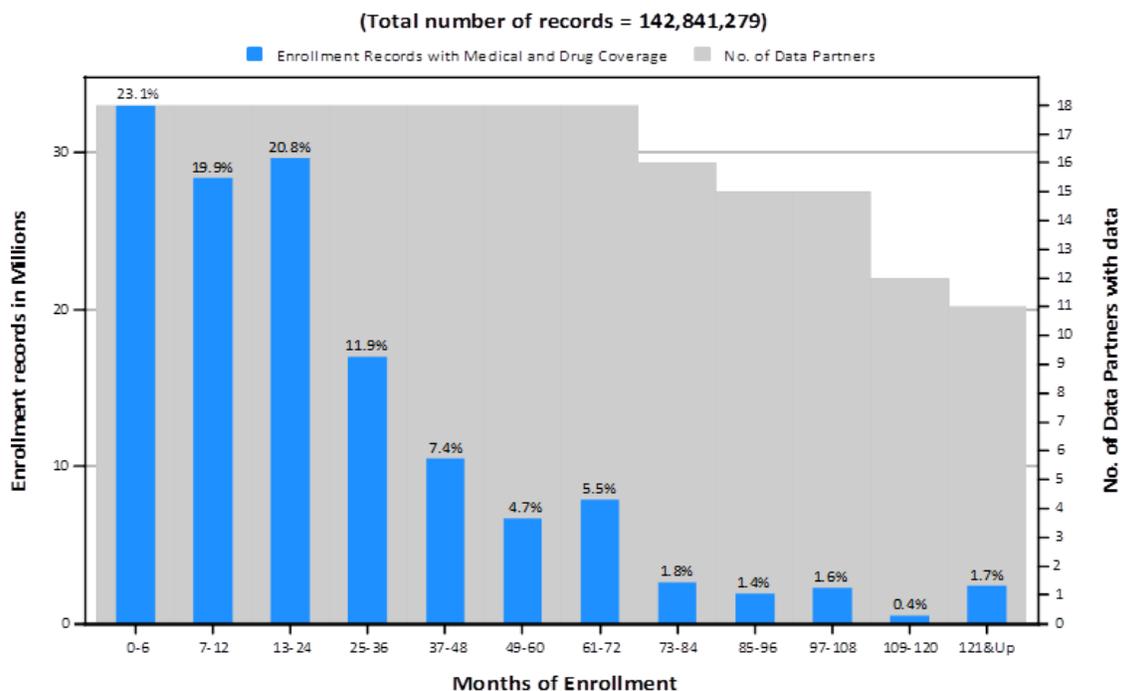


Figure 1. Number of Enrollment Records by Length of Enrollment in the Sentinel database⁶

⁶ Source: Michael D. Nguyen, MD. FDA Sentinel Program Lead.

5. COVARIATES

5.1. Covariates of Interest

The covariates of interest include demographic characteristics (e.g., age, sex, calendar year, and geographic region) and clinical characteristics (e.g., comorbidities and concomitant medications).

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

DDDP determined that code-based approaches to confounding control are adequate for this study. Demographic characteristics (e.g., age, sex, calendar year, geographic region) are able to be assessed in ARIA, which are important covariates for all malignancies. Possible challenges in claims data, especially for certain types of malignancies, include potentially limited covariate information on smoking status, body mass index or obesity, history or family history of malignancy, and also prior use of biologic medications (i.e., some patients in Sentinel will have short look-back periods given the limited long-term follow-up data).

Depending on the type of malignancy, smoking may be a critical covariate (e.g., lung cancer) and obesity may also be a critical risk factor (e.g., colorectal cancer). Furthermore, a history of malignancy or family history of malignancy may be more important for certain types of cancer (e.g., breast cancer). Thus, critical covariate information may be needed to study all types of malignancies, with some covariates being more important than others, depending on the type of malignancy.

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.^{7,8,9} 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.

For all malignancies, some critical covariates (e.g., smoking and obesity) may not be captured well in Sentinel, and therefore, ARIA may not be sufficient to assess the covariates of interest. However, specific to lymphoma, these covariates of concern are not considered to be critical. Therefore, we consider ARIA to be sufficient to assess the covariates of interest, specific to lymphomas.

6. SURVEILLANCE DESIGN / ANALYTIC TOOLS

6.1. Surveillance or Study Design

A simple surveillance to determine the incidence of malignancy among guselkumab was discussed as a possible study design. However, during the SAM, it was discussed that to be more informative,

⁷ Lee PN, Thornton AJ, Hamling JS. Epidemiological evidence on environmental tobacco smoke and cancers other than lung and breast. *Regul Toxicol Pharmacol*. 2016; 80: 134-163.

⁸ Parodi S, Santi I, Marani E. Lifestyle factors and risk of leukemia and non-Hodgkin's lymphoma: a case-control study. *Cancer Causes Control*. 2016; 27(3): 367-375.

⁹ Lauby-Secretan B, Scoccianti C, Loomis D, Grosse Y, Bianchini F, Straif K. Body fatness and cancer – Viewpoint of the IARC Working Group. *N Engl J Med*. 2016; 375(8): 794-798.

we could include comparator cohorts (as mentioned above) to compare malignancy rates for patients receiving guselkumab versus comparable exposures defined as other biologic medications and non-biologic systemic medications.

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

ARIA includes analytic tools for comparative analysis, including Cox proportional hazards regression with confounder control. Propensity score methods can also be used to adjust for differences between patients receiving guselkumab versus other comparator medications. We consider ARIA to be sufficient with respect to the design/analytic tools available to assess the risk of malignancy.

7. NEXT STEPS

ARIA is determined to be insufficient to assess long-term malignancy (i.e., all types), due to limited long-term follow-up, poor validation of certain malignancy types, and incomplete capture of potentially critical confounders. A long-term prospective cohort study would be a more appropriate post-marketing study design to better assess malignancy risk among guselkumab users.

ARIA is considered to be sufficient to assess risk for short-term lymphoma, because lymphomas are reasonably well-validated in claims data, short-term risk is of interest, and the other domains (population, exposure, covariates, and analytic tools) were determined to be sufficient. The next step would be to write a planning brief upon guselkumab's approval, evaluate guselkumab's market uptake yearly, and then conduct a feasibility analysis in ARIA once sufficient uptake is achieved. The feasibility study would include an assessment of the market uptake for guselkumab and the number of patients and person-time available for analysis.

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/s/

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Pregnancy and Lactation Labeling Rule (PLLR) Labeling Review

Date: 4-12-2017

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

Through: John Alexander, M.D., M.P.H.
Deputy Director,
Division of Pediatric and Maternal Health

To: Division of Dermatology and Dental Products

Drug: Guselkumab for injection; BLA 761061

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

Subject: Pregnancy and Lactation Labeling Rule (PLLR) Labeling as part of original BLA

Applicant: Janssen Biotech, Inc.

Materials Reviewed: • Applicant's proposed labeling
• Applicant's review of pregnancy safety data

Consult Question: Please review the Pregnancy and Lactation Labeling Rule (PLLR) Labeling

INTRODUCTION

The applicant submitted an original BLA for guselkumab injection on November 16, 2016. The proposed indication is the treatment of adult patients 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 November 18, 2016, to assist with reviewing the Pregnancy and Lactation subsections of labeling.

BACKGROUND

Product Background

Guselkumab is a new molecular entity; it is a human IgG1 λ monoclonal antibody that binds selectively to human IL-23. Levels of IL-23 are elevated in the skin of patients with plaque psoriasis. Guselkumab exerts clinical effects in plaque psoriasis through blockade of the IL-23 cytokine pathway. The molecular weight is 143,600 Daltons, and the biological half-life is 15-18 days. Guselkumab may increase the risk of infections.

Psoriasis and Pregnancy

Psoriasis affects 2% to 3% of the population, men and women equally.¹ 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.² 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.¹

Pregnancy and Lactation Labeling Rule (PLLR)

On June 30, 2015, the “*Content and Format of Labeling for Human Prescription Drug and Biological Products; Requirements for Pregnancy and Lactation Labeling*,” also known as the Pregnancy and Lactation Labeling Rule (PLLR), took effect.³ The PLLR requirements include a change to the structure and content of labeling for human prescription drug and biologic products with regard to pregnancy and lactation, and a new subsection for information with regard to females and males of reproductive potential. Specifically, the pregnancy categories (A, B, C, D and X) will be removed from all prescription drug and biological product labeling and a new format will be required for all products that are subject to the 2006 Physicians Labeling Rule, to

¹ 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.

² Bangsgaard N, Rørbye C, Skov L et al. Treating Psoriasis During Pregnancy: Safety and Efficacy of Treatments. *Am J Clin Dermatol*. 2015 Oct; 16(5):389-98.

³ Content and Format of Labeling for Human Prescription Drug and Biological Products, Requirements for Pregnancy and Lactation Labeling (79 FR 72063, December 4, 2014).

include information about the risks and benefits of using these products during pregnancy and lactation.

REVIEW

Pregnancy

Nonclinical Experience

A prenatal and postnatal development study conducted in pregnant monkeys at doses up to 30 times the maximum recommended human dose (MRHD), during the period of organogenesis, revealed no evidence of harm to the developing fetus, or to infants through 6 months postpartum. Neonatal deaths were observed in control and treated monkeys at 6- to 30-times the MRHD (*see Data*). The clinical significance of these nonclinical findings is unknown.

Please refer to the toxicology review by Drs. Renqin Duan and Barbara Hill.

Review of Human Pregnancy Data

Applicant's review of pregnancies that occurred in the clinical development program

The clinical development program included 21 reports of pregnancy identified in studies of guselkumab in completed studies in plaque psoriasis, rheumatoid arthritis, or palmoplantar pustulosis, including 9 pregnancies in female subjects exposed to guselkumab participating in these studies and 12 pregnancies in female partners of male subjects exposed to guselkumab participating in these studies.

Maternal pregnancy outcomes included the following:

- 1 abortion (unspecified)
- 2 spontaneous abortions
- 6 were not reported or continuing.

Paternal pregnancy outcomes included the following:

- 1 elective abortion
- 1 spontaneous abortion
- 1 ectopic pregnancy
- 9 were not reported or continuing.

Literature Review

DPMH performed a literature search for information regarding guselkumab and use during pregnancy. No published information was identified.

Summary

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

Intended and unintended exposures during pregnancy will likely occur because plaque psoriasis commonly occurs in females of reproductive potential. In addition, safety data regarding exposure during pregnancy are lacking because pregnant women were excluded during guselkumab's 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 guselkumab's safety in pregnancy.

Lactation

Nonclinical Experience

Guselkumab was not detected in the milk of lactating cynomolgus monkeys. Please refer to the toxicology review by Drs. Renqin Duan and Barbara Hill.

Literature Review

DPMH performed a literature search for clinical information regarding guselkumab and lactation. No published information was identified.

Summary

Guselkumab was not detected in the milk of cynomolgus monkeys. There are no data on the presence of guselkumab in human milk, the effects on the breastfed infant, or the effects on milk production. Maternal human IgG are present in breast milk. Guselkumab, if transferred into breast milk, may be degraded in the gastrointestinal tract of the breastfeeding infant; however, its effects on the breastfed infant are unknown. Therefore, DPMH recommends that the following PLLR risk/benefit statement is included in section 8.2 of labeling:

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

Females and Males of Reproductive Potential

Infertility

Nonclinical Experience

No effects on fertility parameters were identified in female and male guinea pigs that were administered guselkumab at subcutaneous doses up to 100 mg/kg twice-weekly prior to and during the mating period.

Literature Review

DPMH performed a literature search for clinical information regarding guselkumab and effects on fertility. No published information was identified.

Summary

Guselkumab animal fertility studies showed no adverse effects, and there are no human data available. Since there are no data that support an association with infertility effects, Section 8.3, Females and Males of Reproductive Potential, will not be included in guselkumab labeling.

DISCUSSION

Plaque psoriasis is common in females of reproductive potential, and therefore unintended and intended exposures to guselkumab in pregnancy are likely to occur. There are limited data to inform the safety of guselkumab use during pregnancy, and findings of neonatal deaths in monkeys have unknown clinical relevance. Therefore, post-approval studies are needed to characterize guselkumab's safety in pregnancy. DPMH recommends a Post-Marketing

Requirement (PMR) that requires the applicant to perform a pregnancy exposure registry study and a complementary study to assess the safety of guselkumab in pregnant women. 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.⁴ In addition, pregnancy registries allow collection of patient-level detailed data on gestational timing of exposure and potential confounders. 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.⁵ 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.

Recommended language for the PMR is included in Appendix A.

CONCLUSION

The Pregnancy and Lactation subsections of guselkumab labeling were structured to be consistent with the PLLR. DPMH has the following recommendations for guselkumab labeling:

- **8.1 Pregnancy**
 - The “Pregnancy” subsection of guselkumab labeling was formatted in the PLLR format to include “Risk Summary” and “Data” sections.
- **8.2 Lactation**
 - The “Lactation” subsection of guselkumab labeling was formatted in the PLLR format to include the “Risk Summary” section.

DPMH LABELING RECOMMENDATIONS

DPMH discussed our labeling recommendations with DDDP. DPMH recommendations are below and reflect the discussions with DDDP. **See final labeling for all of the labeling revisions negotiated with the applicant.**

⁴ FDA Guidance for Industry Establishing Pregnancy Exposure Registries

⁵ 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>

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

There are no available data on TRADENAME use in pregnant women to inform a drug associated risk of adverse developmental outcomes. Human IgG is known to cross the placental barrier, therefore, TRADENAME may be transmitted from the mother to the developing fetus. (b) (4)

Neonatal deaths were observed (b) (4) at 6- to 30-times the MRHD (*see Data*). The clinical significance of these nonclinical findings is unknown.

All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. The estimated 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 to 4% and 15 to 20%, respectively.

Data

Animal Data

In a pre- and post-natal development toxicity study, pregnant cynomolgus monkeys (b) (4) were administered weekly subcutaneous doses of guselkumab up to 30 times the MRHD from the beginning of organogenesis to parturition. Neonatal monkey deaths occurred in the offspring of 1 (b) (4) control monkey (b) (4) administered guselkumab at 6 times the MRHD (on a mg/kg basis of 10 mg/kg/week) and 3 (b) (4) monkeys administered guselkumab at 30 times the MRHD (on a mg/kg basis of 50 mg/kg/week). (b) (4)

(b) (4). The clinical significance of these findings is unknown. No guselkumab-related effects on functional or immunological development were observed in the infants from birth through 6 months of age.

8.2 Lactation

Risk Summary

There are no data on the presence of guselkumab in human milk, the effects on the breastfed infant, or the effects on milk production. Guselkumab was not detected in the milk of lactating cynomolgus monkeys. Maternal IgG is known to be present in human milk. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for TRADENAME and any potential adverse effects on the breastfed infant from TRADENAME or from the underlying maternal condition.

Appendix A-PMR Language Recommendation

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 guselkumab 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.”

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/3626f1.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/

LEYLA SAHIN
04/12/2017

JOHN J ALEXANDER
04/12/2017

**CONSULTATIVE REVIEW AND EVALUATION OF CLINICAL DATA
CONSULT #11629**

Consultant Reviewer: John Umhau, MD, MPH
Medical Officer
Division of Psychiatry Products

Consultation Requestor: Melinda McCord, MD
Medical Officer
Division of Dermatology and Dental Products

Subject of Request: BLA 761061/Guselkumab SC Injection

Date of Request: November 21, 2016

Date Received: November 21, 2016

Desired Completion Date: April 3, 2017

I. Background

Janssen Research and Development submitted BLA 761061 to the Division of Dermatology and Dental Products (DDDP) for guselkumab subcutaneous injection in the treatment of patients with moderate to severe plaque psoriasis who are candidates for systemic therapy or phototherapy. Guselkumab is a human IgG1 λ monoclonal antibody that binds to human IL-23.

The rates of psychiatric morbidity, including depression and suicidal behavior, are higher among patients with psoriasis relative to the general population.^{1,2} The reasons for this are obscure, but may be due to inflammatory mediators (i.e. cytokines) implicated in the pathogenesis of suicide and related psychiatric conditions.^{3,4} In previous psoriasis trials, suicidal ideation and behavior (SIB) events were increased with brodalumab, while symptoms of depression were reduced by etanercept, an effect not explained by a reduction in psoriasis symptoms.^{5,6}

¹ Olivier, Chosidow, et al. "The risk of depression, anxiety, and suicidality in patients with psoriasis: a population-based cohort study." *Archives of dermatology* 146.8 (2010): 891-895.

² Connor, Cody J., Vincent Liu, and Jess G. Fiedorowicz. "Exploring the physiological link between psoriasis and mood disorders." *Dermatology research and practice* 2015 (2015).

³ Brundin, Lena, et al. "The role of inflammation in suicidal behaviour." *Acta Psychiatrica Scandinavica* 132.3 (2015): 192-203.

⁴ Raison, Charles L., Lucile Capuron, and Andrew H. Miller. "Cytokines sing the blues: inflammation and the pathogenesis of depression." *Trends in immunology* 27.1 (2006): 24-31.

⁵ Danesh, Melissa J., and Alexa B. Kimball. "Brodalumab and suicidal ideation in the context of a recent economic crisis in the United States." *Journal of the American Academy of Dermatology* 74.1 (2016): 190-192.

Clinical trials were conducted under IND 105004 and did not prospectively assess for the emergence of SIB. Therefore, DDDP requested the Applicant to conduct a retrospective analysis for the occurrence of SIB in their clinical trials. DDDP has requested that the Division of Psychiatry Products (DPP) evaluate the adequacy and findings of this analysis, assess other psychiatric adverse events in the clinical trials, and provide any recommendations for the labeling of psychiatric adverse reactions for this product.

II. Review Of Clinical Data

A. Clinical Trials Database

The Applicant assessed the occurrence of SIB from one global Phase 2 study (CNTO1959-PSO2001) and three global Phase 3 studies (CNTO1959-PSO3001, CNTO1959-PSO3002, and CNTO1959-PSO3003) using June 30, 2016, as the safety cutoff date. A total of 1748 subjects received guselkumab in these trials. The study designs are summarized below.

Subjects were excluded from guselkumab clinical trials if there was a history or presence of signs or symptoms of “severe, progressive, or uncontrolled psychiatric disturbance.” Subjects with a history of SIB were not necessarily excluded.

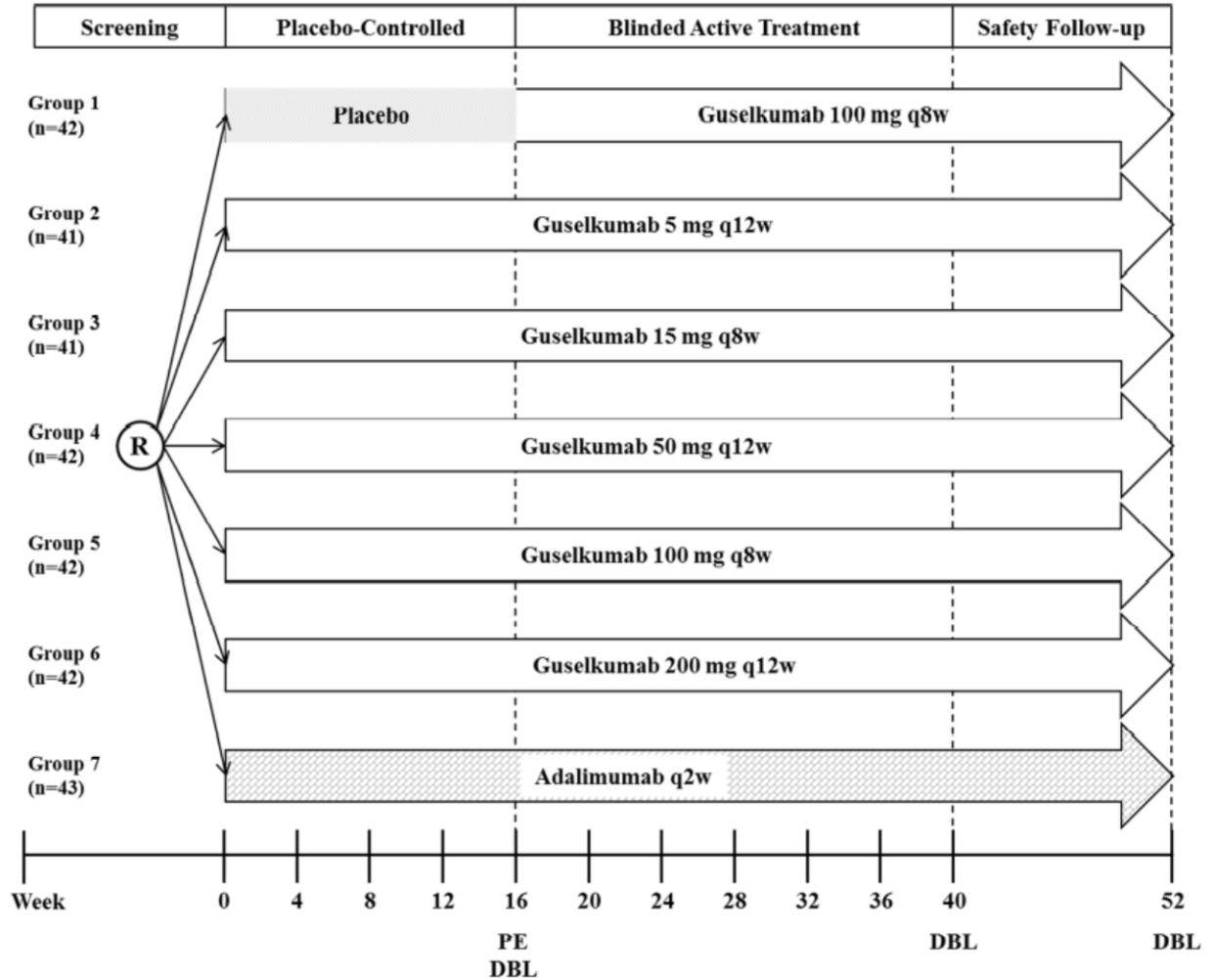
Only Study CNTO1959-PSO3002 systematically monitored measures related to mental health.

Study CNTO1959-PSO2001

Study CNTO1959PSO2001 was a Phase 2, randomized, placebo- and active-comparator (adalimumab) controlled, parallel group, multicenter, dose-ranging study of guselkumab in subjects with moderate to severe plaque psoriasis. See Figure 1.

⁶ Tyring, Stephen, et al. "Etanercept and clinical outcomes, fatigue, and depression in psoriasis: double-blind placebo-controlled randomised phase III trial." *The Lancet* 367.9504 (2006): 29-35.

Figure 1: Schematic Overview of Study CNTO1959-PSO2001:

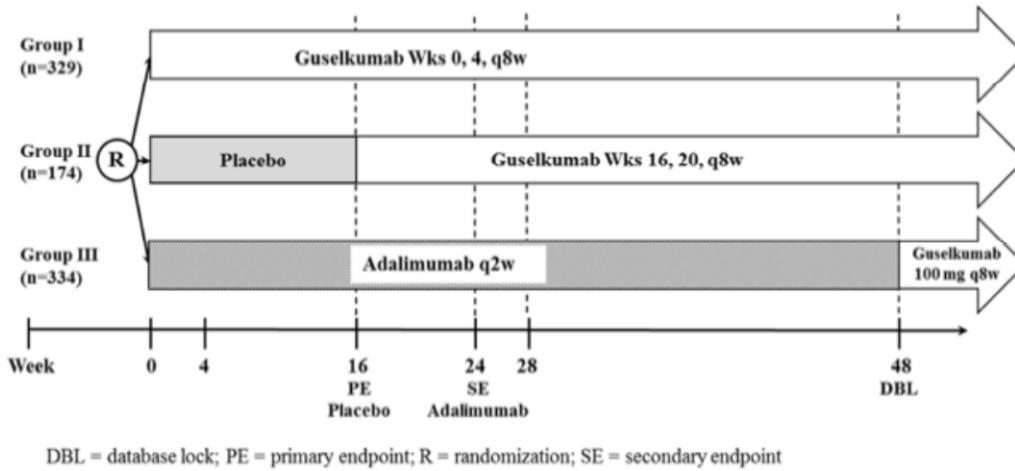


DBL = database lock; PE = primary endpoint; R = randomization; q8w = every 8 weeks; q12w = every 12 weeks

Study CNTO1959-PSO3001

Study CNTO1959PSO3001 was a Phase 3 study to evaluate the efficacy and safety of guselkumab in subjects with moderate to severe plaque psoriasis. See Figure 2.

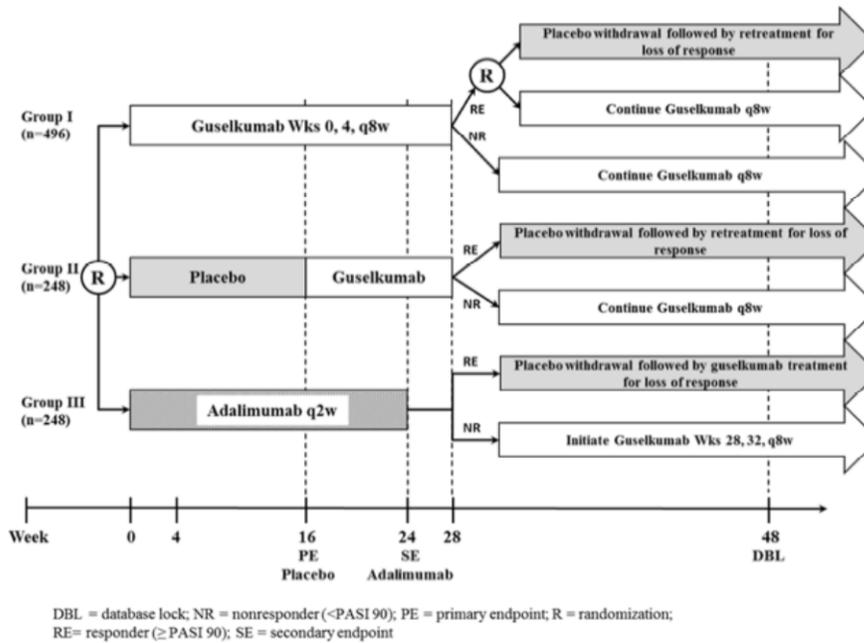
Figure 2: Schematic Overview of Study CNTO1959-PSO3001



Study CNTO1959-PSO3002

Study CNTO1959-PSO3002 was similar to Study CNTO1959-PSO3001. See Figure 3.

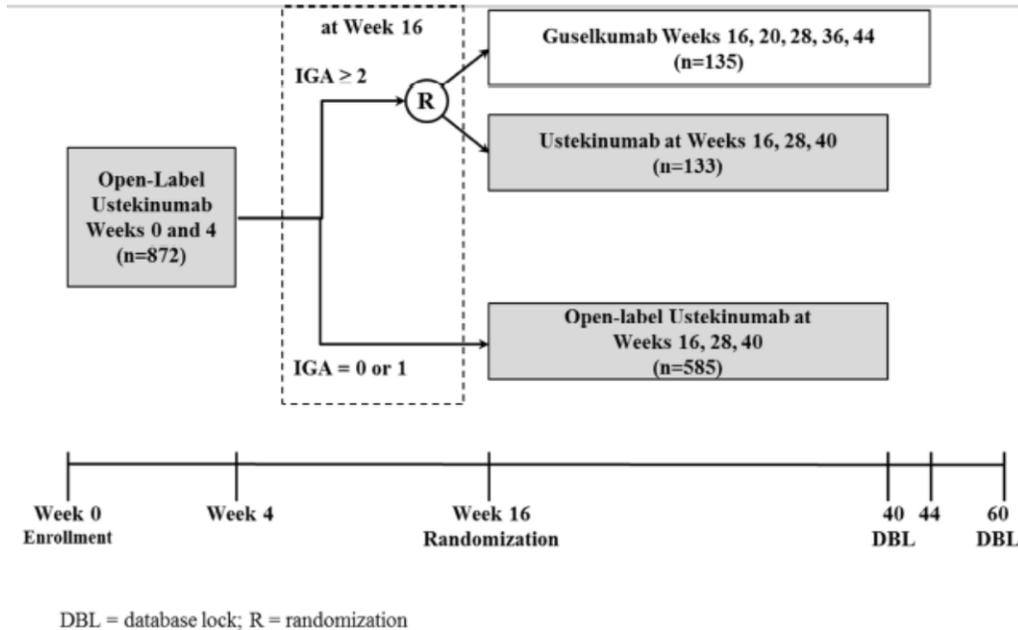
Figure 3: Schematic Overview of Study CNTO1959-PSO3002



Study CNTO1959-PSO3003

Study CNTO1959-PSO3003 was a Phase 3 double blind study evaluating the efficacy and safety of guselkumab in subjects with moderate to severe plaque psoriasis and an inadequate response to ustekinumab. See Figure 4.

Figure 4: Schematic Overview of study CNTO1959-PSO3003



B. Retrospective Examination for Suicidal Ideation and Behavior

The Applicant conducted a search for all treatment-emergent adverse event terms containing full or partial word combinations suggestive of self-injurious behavior, as described by Posner.⁷ For this analysis, the Applicant searched adverse event data from the trials CNTO1959-PSO2001, CNTO1959-PSO3001, CNTO1959-PSO3002, and CNTO1959-PSO3003 to create an adjudicated suicidality adverse events analysis dataset (ADSUIADJ). A completely blinded listing of the resulting 321 events was reviewed by four board-certified psychiatrists and clinical psychologists who assigned a score to each event using the Columbia Classification Algorithm of Suicide Assessment (C-CASA). This blinded review identified three episodes of SIB after elimination of items that were clearly false positives: one adverse event coded to suicidality (Suicidal Ideation) for guselkumab and two occurrences of suicidal behavior associated with the active comparator, adalimumab.

When the Applicant extended the observation period of the pooled data set through week 48, the rates of suicidal ideation and behavior per 100 subject-yrs (95% CI) were 0.10 (0.00, 0.57) for guselkumab and 0.43 (0.05, 1.57) for adalimumab.

⁷ Posner, Kelly, et al. Columbia Classification Algorithm of Suicide Assessment (C-CASA): classification of suicidal events in the FDA's pediatric suicidal risk analysis of antidepressants. *American Journal of Psychiatry* 2007;164(7): 1035-1043.

In addition, after the above safety cutoff date, the Applicant submitted preliminary information about the death of a 43 year old male in Study CNTO1959-PSO3001 who was receiving open label guselkumab. This death occurred about one week after his Week 68 visit as a result of a probable suicide. Prior to the study, at screening, the subject was being treated with citalopram for depression. This was stopped but restarted about two months prior to his suicide because of depression.

Reviewer's Comment

With Dr. Douglas Warfield (Associate Director Biomedical Informatics – Division of Psychiatry Products), I reviewed the Search Strategy, which is described in the Statistical Analysis Report Suicidal Ideation and Behavior) and it seems appropriate. The Applicant provided adequate collection, tabulations, and analyses for the FDA's requested retrospective suicide analyses (C-CASA) for guselkumab treatment of patients with psoriasis.

I conducted my own analysis of the ae.xpt datasets for these four trials to identify adverse events for which the investigator term suggested SIB using the following search strings: "attempt", "cut", "gas", "hang", "hung", "jump", "mutilat-", "overdos-", "self damag-", "self harm", "self inflict", "self injur-", "shoot", "slash", "suic-." After elimination of obvious false positives, I identified the same cases as those identified by the Applicant's retrospective analysis.

In the end, I found no statistically significant risk for SIB associated with guselkumab compared to placebo.

C. Review of Other Psychiatric Adverse Events

The reporting rates for other psychiatric adverse events were examined within the initial 16 week, randomized, placebo-controlled phases of the pool of studies CNTO1959-PSO3001 and CNTO1959-PSO3002. These studies were chosen because they had similar designs, including an initial randomized, placebo-controlled phase. The ae.xpt tabulations for these studies were searched for adverse events (AEDECOD) in the Psychiatric Disorders SOC with a start day between Study Day 1 and 112, inclusive. Similar terms (e.g., depression and major depression) were combined. The number of events and rates calculated using JMP are shown in Table 1 below.

This review of adverse event data from these two trials revealed few psychiatric adverse events and no substantially increased risk of psychiatric events with guselkumab compared to placebo.

Table 1: Incidence (N(%)) of Non-SIB Psychiatric Adverse Events (Placebo-Controlled Phases of CNTO1959-PSO3001 and PSO3002)

Adverse Event	Guselkumab N=825	Placebo N=422	Adalimumab N=582
Anxiety	1 (0.1%)	2 (0.5%)	3 (0.5%)
Depression	1 (0.1%)	0 (0.0%)	2 (0.3%)
Insomnia	1 (0.1%)	0 (0.0%)	2 (0.3%)
Libido Decreased	0 (0.0%)	1 (0.2%)	1 (0.2%)
Psychotic Disorder	1 (0.1%)	0 (0.0%)	0 (0.0%)
Derealization	1 (0.1%)	0 (0.0%)	0 (0.0%)

In addition, Study CNTO1959-PSO3002 assessed two self-report measures: the Hospital Anxiety and Depression Scale (HADS) which quantifies depression and anxiety and the Short Form-36 (SF-36) which includes questions about anxiety and depression but not suicide or other psychiatric events. The Applicant reported significantly greater mean improvement from baseline to Week 16 in the guselkumab group compared to placebo in the SF-36 mental component (5.659 vs 0.568, $p < 0.001$). Also, subjects in the guselkumab group had a significantly greater mean improvement from baseline to Week 16 compared to placebo in the HADS anxiety score (-1.1 vs -0.2, $p < 0.001$) and depression score (-1.6 vs -0.1, $p < 0.001$).

III. Conclusions and Recommendations

In summary, although these data are limited by the small sample size, the small number of SIB events, and the lack of prospective measurement, they do not suggest an increased risk of SIB or psychiatric adverse effects with guselkumab in patients with plaque psoriasis that would justify prominent labeling of suicidal ideation or behavior or other psychiatric adverse events.

Currently available pharmacovigilance methods lack sensitivity to detect SIB during the post marketing period. Therefore, future clinical trials should include a prospective evaluation of suicidal ideation, such as the Columbia-Suicide Severity Rating Scale (C-SSRS).

For additional information, please see:

<https://www.fda.gov/downloads/drugs/guidances/ucm225130.pdf>.

Please let us know if we may be of further assistance.

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/s/

JOHN C UMHAU
04/05/2017

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04/10/2017

MITCHELL V Mathis
04/10/2017

CLINICAL OUTCOME ASSESSMENT (COA) CONSULT REVIEW

COA CONSULT TRACKING NUMBER	C2016280
BLA NUMBER	761061
REFERENCED IND FOR NDA/BLA	105004
ESTABLISHED NAME (TRADE NAME)	Guselkumab
APPLICANT	Janssen Research & Development, LLC.
INDICATION	Treatment of moderate to severe plaque psoriasis
LETTER DATE/SUBMISSION NUMBER	November 16, 2016/SDN 1
PDUFA GOAL DATE	July 16, 2017
DATE OF CONSULT REQUEST	November 21, 2016
REVIEW COMPLETION DATE	April 4, 2017
REVIEW DIVISION	Division of Dermatology and Dental Products
MEDICAL REVIEWER/TEAM LEADER (TL)	Melinda McCord/Gordana Diglisic
REVIEW DIVISION PM	Matthew White
PRIMARY COA REVIEWER	Yasmin Choudhry
COA TL	Selena Daniels
ASSOCIATE DIRECTOR, COA STAFF	Elektra Papadopoulos
INSTRUMENT	Psoriasis Symptom and Sign Diary
COA TYPE	Patient-reported outcome
ENDPOINT(S) CONCEPT(S)	Psoriasis sign and symptom severity
INTENDED POPULATION(S)	Adult patients with moderate to severe plaque psoriasis
PLEASE CHECK ALL THAT APPLY:	<input type="checkbox"/> Rare Disease/Orphan Designation <input type="checkbox"/> Pediatric

Clinical Outcome Assessment Review

Yasmin Choudhry, M.D.

BLA 761061

Guselkumab

Psoriasis Symptoms and Signs Diary (symptom and sign severity)

A. EXECUTIVE SUMMARY

This Clinical Outcome Assessment (COA) review is provided as a response to a request for consultation by the Division of Dermatology and Dental Products (DDDP) regarding BLA 761061 guselkumab for the treatment of moderate to severe plaque psoriasis.

The Applicant used a patient-reported outcome (PRO), the Psoriasis Symptom and Sign Diary (PSSD) Symptom domain for the measurement of psoriasis symptom severity in their registration trials (Studies CNT01959PSO3001 [VOYAGE 1] and CNT01959PSO3002 [VOYAGE 2]):

The subject of this review is restricted to the PSSD per the Division's request.

The proposed targeted PRO-related labeling claims are:

Greater improvements in psoriasis symptoms (itch, pain, stinging, burning and skin tightness) [REDACTED] (b) (4)
[REDACTED] *at Week 16 in TRADENAME compared to placebo were observed in both studies based on the Psoriasis Symptoms and Signs Diary (PSSD). Greater proportions of subjects on TRADENAME compared to adalimumab achieved a PSSD symptom score of 0 (symptom free)* [REDACTED] (b) (4)
[REDACTED] *at Week 24 in both studies* [REDACTED] (b) (4)
[REDACTED]

A full Evidence Dossier was submitted to support the development of the PSSD. This review focused on whether the PSSD Symptom domain was fit-for-purpose in the context of this particular drug development program to assess psoriasis symptom severity in the clinical trial.

The review concludes that based on the Applicant's qualitative and quantitative evidence presented in the Evidence Dossier, the PSSD Symptom domain appropriately measures symptom severity and appears to be fit for purpose for the drug development program. The PSSD Symptom domain evaluates the following symptoms: *Itch, pain, stinging, burning and skin tightness*. Qualitative data supports the importance and relevance of these symptoms from the patient's perspective. The concerns for use of transformed scores were mitigated by the endpoint analysis (proportion of subjects who achieve a score of 0 at Week 24). Additionally, a cumulative responder analysis in graph form shows a clear separation between the treatment arms and the placebo arm at a score change of 40 points (on a 0-100 scale).

B. BACKGROUND

Regulatory History

April 15, 2014 Meeting Minutes: FDA recommended that the Applicant:

Clinical Outcome Assessment Review

Yasmin Choudhry, M.D.

BLA 761061

Guselkumab

Psoriasis Symptoms and Signs Diary (symptom and sign severity)

- Modify the Psoriasis Symptom and Sign Diary (PSSD) to include separate sub-scales for psoriasis symptoms (itching, pain, stinging, burning and skin tightness) and psoriasis signs (skin dryness, cracking, scaling, shedding or flaking, redness and bleeding).
- Provide rationale for including “pain/burning/ stinging” and “skin tightness” as symptoms and provide a description of the percentage of subjects who spontaneously mentioned “pain/burning/ stinging” and “skin tightness” in the qualitative research.
- Consider the 24-hour version to minimize recall effect and to avoid requiring patients to mentally average symptoms across a long period of time. This is not a regulatory requirement, but may improve the ability of the instrument to detect treatment effect on pruritus.

Materials reviewed:

- PSSD Evidence dossier (SDN 1)
- DDDP Consult Request dated November 21, 2016
- FDA documents:
 - Information Request dated February 13, 2017; and Sponsor’s Response (SDN 16) received February 21, 2017
 - Meeting Minutes dated April 15, 2014

C. CLINICAL OUTCOME ASSESSMENT REVIEW

1 CONTEXT OF USE

1.1 Clinical Trial Population

The clinical trial target population was adult men or women with a diagnosis of moderate to severe plaque psoriasis (with or without psoriatic arthritis) for at least six months before the first administration of study drug defined by Investigator’s Global Assessment (IGA) ≥ 3 , Psoriasis Area and Severity Index (PASI) ≥ 12 , and involved body surface area (BSA) $\geq 10\%$. Participants were candidates for either systemic therapy or phototherapy for psoriasis, and might have previously received some systemic therapies or phototherapy for psoriasis.

Subjects with non-plaque forms of psoriasis or with possible drug-induced psoriasis were excluded.

1.2 Clinical Trial Design

Two identical studies (CNT01959PSO3001; [VOYAGE 1]; CNT01959PSO3002 [VOYAGE 2]) that were multicenter, randomized, and double-blind were conducted to evaluate the efficacy and safety of guselkumab in subjects with moderate to severe plaque-type psoriasis compared with placebo and adalimumab. The double-blind treatment period extended from Week 0 through Week 44. An open-label guselkumab treatment period was to begin after Week 48 and extended through Week 160.

Clinical Outcome Assessment Review

Yasmin Choudhry, M.D.

BLA 761061

Guselkumab

Psoriasis Symptoms and Signs Diary (symptom and sign severity)

The Clinical review provides further details of the study designs and results. For study synopses clinical study reports, see SDN 1.

Reviewer comments: The Applicant stated in their 48-Week Clinical Study Report (Section 6.6.2.1, page 91 of CNTO1959PSO300, VOYAGE 1; Section 6.6.2.1, page 117 of CNTO1959PSO3002, VOYAGE 2) that there was initial technical difficulties associated with the electronic device (erPRO/eDiary/LogPad) and with data transmission, resulting in missing baseline PSSD scores for 22% (185/837) randomized subjects. Because of this, the Applicant pre-defined their analysis population to subjects who had baseline PSSD scores; subjects without baseline PSSD scores were excluded from all PSSD analyses. The baseline PSSD score was defined as the average score of at least 4 days out of the 7 days prior to the Week 0 visit. The Applicant did assess the pattern of the missing baseline PSSD data, and concluded that overall subjects with missing baseline PSSD scores had similar median psoriasis disease duration and IGA scores as subjects with baseline PSSD scores. The Applicant concluded that missing baseline PSSD data occurred randomly in VOYAGE 1 most likely because of technical LogPad issues rather than specifically within an identifiable subgroup of subjects.

1.3 Endpoint Hierarchy and Definition

The co-primary and major secondary efficacy endpoints in order of pre-specified testing hierarchy were:

Concepts	Endpoints	Instrument
Co-Primary Efficacy Endpoints		
Severity of psoriasis	Cleared (0) or minimal (1)	Investigator Global Assessment (IGA)
Extent and severity of psoriasis	90% response	Psoriasis Area Severity Index (PASI)
Major Secondary Efficacy Endpoints		
Severity of psoriasis	Proportion of subjects who achieve an IGA of 0 (Weeks 24, 48)	IGA
Severity of psoriasis	Proportion of subjects who achieve an IGA of 0 or 1 (Weeks 16, 24, 48)	IGA
Extent and severity of psoriasis	Proportion of subjects who achieve a PASI-90 (Weeks 16, 24, 48)	PASI
Health-related quality of life	Change from baseline at Week 16	Dermatology Life Quality Index (DLQI)
Psoriasis symptom	Change from baseline at Week 16	Psoriasis Symptom and Sign

Clinical Outcome Assessment Review

Yasmin Choudhry, M.D.

BLA 761061

Guselkumab

Psoriasis Symptoms and Signs Diary (symptom and sign severity)

severity	Proportion of subjects who achieve a score of 0 at Week 24	Diary (PSSD) Symptom domain
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1.4 Labeling or promotional claim(s) based on the COA

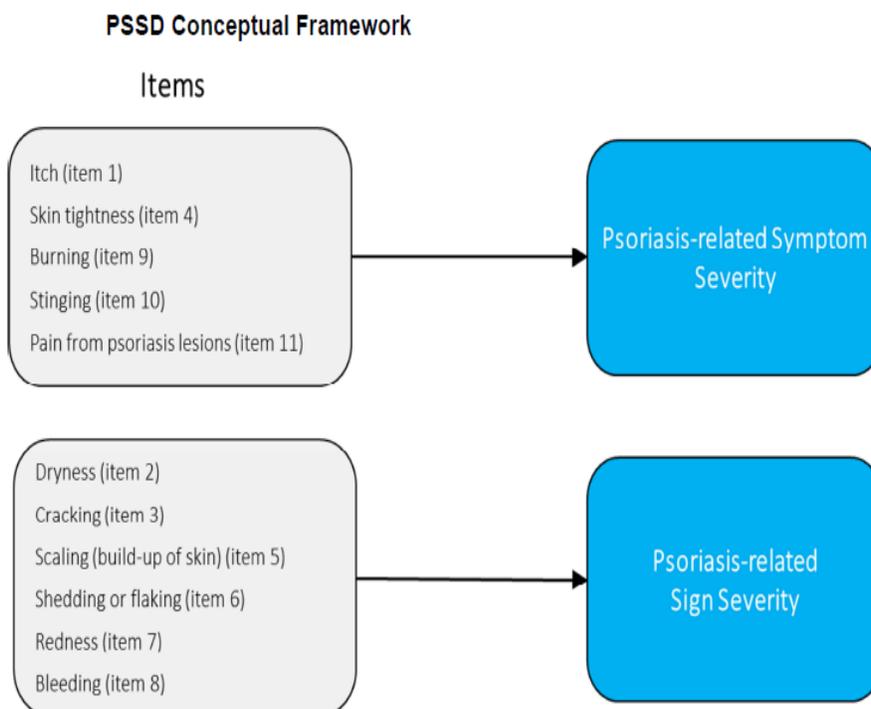
The Applicant seeks the following PRO-related targeted labeling claim:

Greater improvements in psoriasis symptoms (itch, pain, stinging, burning and skin tightness) [REDACTED] (b) (4) at Week 16 in TRADENAME compared to placebo were observed in both studies based on the Psoriasis Symptoms and Signs Diary (PSSD). Greater proportions of subjects on TRADENAME compared to adalimumab achieved a PSSD symptom score of 0 (symptom free) [REDACTED] (b) (4) at Week 24 in both studies [REDACTED] (b) (4).

Reviewer comment: *Based on discussion with the biostatistical reviewer, the PSSD Sign domain was not a major secondary endpoint (alpha-controlled).*

2 CONCEPT OF INTEREST (COI) AND CONCEPTUAL FRAMEWORK

The PSSD conceptual framework is as follows:



Clinical Outcome Assessment Review

Yasmin Choudhry, M.D.

BLA 761061

Guselkumab

Psoriasis Symptoms and Signs Diary (symptom and sign severity)

3 CLINICAL OUTCOME ASSESSMENTS

Psoriasis Symptom and Sign Diary (PSSD)-24 hour version:

See Appendix A: PSSD-24 hour paper and Appendix B: PSSD-24 hour electronic

The PSSD-24 hour scale includes 11 items to assess severity of signs and symptom of psoriasis and consists of two domains:

- Symptoms: *itch, pain, stinging, burning and skin tightness*
- Signs: *skin dryness, cracking, scaling, shedding or flaking, redness and bleeding*

The response options are on a numerical rating scale (NRS) from 0= absent to 10 =worst imaginable. The recall period is 24 hours. A higher score indicates more severe symptoms and signs.

Psoriasis Symptom and Sign Diary (PSSD)-7 day version:

See Appendix C: PSSD-7 day electronic and Appendix D: PSSD-7 day paper.

The PSSD-7 day version is comprised of two parts:

- Part 1 includes 11 items that assess severity of symptoms and signs of psoriasis. The response options are 0= Absent to 10= Worst imaginable.
- Part 2 includes 11 items that assess frequency of symptoms and signs of psoriasis on a 5-point scale ranging from “None (0 days) of the days to “All (7 days) of the days.”

The recall period is past 7 days. A higher score indicates more severe symptoms and signs.

The instructions for patients are included in both versions.

Reviewer comments: The PSSD-24 hour scale was used for the major secondary endpoint. The PSSD-7 day scale was used in the open label portion of the clinical trial(s) (after Week 48). The data from the open label study was used to conduct additional validation analyses for the 7 day scale to generate a responder definition that could be applied to the 24 hour scale. Refer to Section 5 of this review in regards to equivalency data for the two measures.

Scoring:

PSSD-24 hour and PSSD-7 day versions: For each version of the scale, two summary scores are derived, a psoriasis symptom summary score and a psoriasis sign summary score.

- PSSD-24 hour version: Each individual item score over 7 days is averaged into a weekly score. Daily scores of at least 4 days out of 7 days prior to a visit (either consecutive or non-consecutive) are required to derive a weekly score otherwise data are considered missing for that week.

Clinical Outcome Assessment Review

Yasmin Choudhry, M.D.

BLA 761061

Guselkumab

Psoriasis Symptoms and Signs Diary (symptom and sign severity)

- PSSD-7 day version: The raw score at each scheduled visit was used as an item score (range from 0-10).

Transformed score:

The raw scores scores from the Symptom and Sign domains are transformed to a 0-100 scale.

- For the symptom score: Daily symptom item scores were averaged when at least 3 items ($\geq 50\%$ of 5 items) on this scale were answered, then the average value was converted into 0-100 scoring such that symptom score = average value of evaluable items x 10, with 0 representing the least severe and 100 the most severe.
- For the sign score: Daily items scores were averaged when at least 3 items ($\geq 50\%$ of 6 items) on this scale were answered, then, the average value was converted into 0-100 scoring such that sign score = average value of evaluable items x 10, with 0 representing the least severe and 100 the most severe.

Similar procedures were used to calculate severity and frequency scores from the PSSD-7 day scale.

4 CONTENT VALIDITY

The development of the PSSD-24 hour and 7 day scales were based on a review of published literature, patient, and clinician input.

This section of the review provides a synopsis of the results. The study design and full findings are in the Evidence Dossier (Section 5.0 of the Evidence Dossier).

The initial item generation and development of the draft version of the 14-item PSSD resulted from concept elicitation interviews in patients with moderate to severe psoriasis, input from clinical experts, and a literature review of the existing PRO instruments (see Table 10: Rationale for item selection in Section 5.5 of the Evidence Dossier). Cognitive interviews on the 14-item draft PSSD were then conducted to confirm comprehension. Three (b) (4) of the fourteen items were dropped after 3 waves of cognitive interviews, and minor modifications on instructions and format were made after review for translatability and migration to the electronic format. This resulted in a final draft PSSD which included 11 items. The concept elicitation and cognitive interviews are further discussed below.

Concept elicitation interviews

Concept elicitation interviews (face-to-face; each 60 minutes long) were conducted in 20 individuals (18 years and older) with moderate to severe psoriasis at three United States (U.S.) Sites (private dermatology treatment centers). The mean age of participants was 40 years, and the mean number of years since diagnosis was 20 years. Approximately, half of the participants had moderate plaque-psoriasis and half had severe plaque-psoriasis (based on the body surface area [BSA] ratings: mild= $\leq 3\%$; moderate= $3-10\%$; severe= $>10\%$). All interviews were audio-recorded and transcribed; and the transcripts were coded. Commonly reported symptoms are shown in the table below:

Clinical Outcome Assessment Review

Yasmin Choudhry, M.D.

BLA 761061

Guselkumab

Psoriasis Symptoms and Signs Diary (symptom and sign severity)

Commonly-reported Symptoms Emerging from Concept Elicitation Interviews

Symptom	% Reporting
Itching	85%
Soreness/Pain	80%
Flakiness	75%
Redness	70%
Dry/Scaly Skin	70%
Hot/Burning/Stinging Sensation	60%
Cracked/Bleeding Skin	50%

Saturation of symptoms (when no new symptoms were mentioned) was achieved by the sixth interview.

Based on the qualitative evidence, the concepts of pain, stinging, burning and skin tightness were included as separate, individual items in the final version of PSSD instrument based on further evidence from patients and expert opinion. Some of the patient quotes are as follows:

Concept	Patient quote
Itch	<i>I would just say you know something that causes you to scratch your skin, an irritating feeling constant (002-02)</i>
Skin tightness	<i>It feels like my skin is drawn in (002-004) I guess to me that would be a lack of elasticity of your skin (001-05)</i>
Burning	<i>Burning that's more like, I don't know, it's not as tolerable as stinging. Burning is more painful (002-02) Well if something burns, it's like you strike a match and put it out and stick it up to your skin. That burns (002-08)</i>
Stinging	<i>Stinging is more like a bee sting (002-09) Stinging comes from usually from within. So burning is outside and stinging is inside (002-08)</i>
Pain	<i>It hurts to move the area that it's in or it hurts to touch it (002-05)</i>

Reviewer comment: FDA initially had questioned the sponsor whether patients can differentiate between the concepts pain, stinging and burning. The Applicant's qualitative evidence is sufficient to determine that these concepts are separate concepts. Note that a labeling claim for the item pain was approved for Cosentyx BLA 125504; and a labeling claim for pain, stinging, burning was approved for Brodalumab BLA 761032. Additionally, at the Psoriasis Patient Focused Drug Development meeting, this reviewer (who was a panelist at this meeting) asked patients in the audience whether they considered pain, stinging and

Clinical Outcome Assessment Review

Yasmin Choudhry, M.D.

BLA 761061

Guselkumab

Psoriasis Symptoms and Signs Diary (symptom and sign severity)

burning separate concepts or the same. At least three psoriasis patients from the audience stated that they considered these concepts as distinct from each other.

Although there were minimal patients reporting the experience of skin tightness, there were many patients who endorsed this item at baseline in the registration trials.

Cognitive Interviews

Three waves of cognitive interviews with 19 participants with mild, moderate, or severe plaque psoriasis from two dermatology clinics in the U.S. were conducted to obtain feedback on the draft 14-item version of the PSSD. The results are as follows:

Content of PSSD: When subjects were asked if there were any important symptoms missing, 72% subjects did not feel there were any missing symptoms.

Response options:

- All participants were able to understand the severity response options, and were able to find a response for every severity items.
- Sixty three percent of the participants thought the number of response options for severity were appropriate, while 38% (n=6) thought the response options were too many.
- All participants found the words describing the anchors in the severity responses (i.e., “absent” and “worst imaginable”) to be helpful.

An 11-point NRS was implemented to be better able to detect small, but meaningful, changes in the severity of symptoms. The final PSSD-24 hour scale includes only the severity response options, while the PSSD-7 day scale has both severity and frequency response options.

Recall period:

- Ninety five percent (n=18) of the participants felt they were accurate in remembering their symptoms over the past 24 hours.
- Fifty percent of subjects would prefer to complete it less frequently than every 24 hours, while 50% felt the 24 hour recall period was “just right.”

Preferred time to complete the PSSD:

- Sixty three percent (n=12) of the participants preferred to complete the diary at night or in the evening; and 71% preferred to complete the diary in the evening.

Feedback on PSSD-7 day scale:

- Only four participants were asked which of the two versions of the PSSD (24 hour; 7 day) would they prefer. All four participants indicated that although they would prefer the 7 day version, but they would be more accurate in reporting on a daily basis.
- Of the 11 participants who were asked about the accuracy of the recall period, 69% thought they would be more accurate in reporting on a daily basis.

Clinical Outcome Assessment Review

Yasmin Choudhry, M.D.

BLA 761061

Guselkumab

Psoriasis Symptoms and Signs Diary (symptom and sign severity)

- Sixty-two percent (n=8) did not think their symptoms would vary day-to-day, while 23% (n=3) thought they would vary, and 15% (n=2) didn't know if they would vary.

Additional cognitive interviews were conducted in five patients (with similar demographics as the original interviews) with moderate to severe psoriasis to confirm the final instructions, items, and response options of the final PSSD. The results of the interviews are as follows:

- The additional interviews confirmed that patients understood the instructions and recall period appropriately for the PSSD-7 day scale. Further, two patients noted that they may recall more accurately with a weekly recall and one patient reported their accuracy would be the same whether they answered daily or weekly. Please refer to Appendix G of the Evidence Dossier for more details on these results (Content Validity Semi-Structured Interview Guide).

Reviewer comment: The concept elicitation interviews supported the symptoms included in the Symptom domain. The item skin tightness was only reported by 10% of the participants.

5 OTHER MEASUREMENT PROPERTIES (RELIABILITY, CONSTRUCT VALIDITY, ABILITY TO DETECT CHANGE)

The Evidence Dossier refers to two studies (Study 1 and Study 2) under which the measurement properties of the two PSSD versions (24 hour recall; 7-day recall) were evaluated:

- Study 1: A prospective, observational, validation study of 106 adults (≥ 18 years of age) with moderate to severe plaque psoriasis, conducted at approximately 8 dermatology clinics in the U.S. Participants eligible for the study were similar to those of the Phase 3 clinical trials (see Section C1.2 above). Participants were randomized into two groups:
 - Group A: Participants were asked to complete the PSSD-24 hour scale daily for 14 days (Days 1 to 14) at the same time each day.
 - Group B: Participants were asked to complete the PSSD-24 hour scale daily for 7 days (Days 8 to 14) at the same time each day.

All participants (see table below) were provided with a date and time stamper to use when completing the PSSD. Participants also completed the PSSD-7 day scale, Psoriasis Impact Questionnaire (PIQ), DLQI, 36-item Short Form Health Survey (SF-36), and Patient Global Impression (PGI) at baseline and Days 7 and 14.

Clinical Outcome Assessment Review

Yasmin Choudhry, M.D.

BLA 761061

Guselkumab

Psoriasis Symptoms and Signs Diary (symptom and sign severity)

Study 1 Demographic and Clinical Characteristics

Characteristic		Overall	Group A	Group B	Significance: A vs. B
	N	106	55	51	--
Age (years)	Mean (SD)	50.1 (12.1)	48.4 (12.5)	51.8 (11.6)	.151
Sex (n, %)	Male	41 (38.7)	17 (30.9)	24 (47.1)	.111
	Female	65 (61.3)	38 (69.1)	27 (52.9)	
Race	White	76 (71.1)	38 (69.1)	38 (74.5)	.448
	Black or African American	7 (6.6)	3 (5.5)	4 (7.8)	
	Native American	1 (0.9)	1 (1.8)	0 (0.0)	
	Asian	6 (5.7)	4 (7.3)	2 (3.9)	
	Hispanic	13 (12.3)	6 (10.9)	7 (13.7)	
	Other	3 (2.8)	3 (5.5)	0 (0.0)	
Psoriasis disease duration (yrs)	Mean (SD)	16.8 (12.6)	15.8 (12.6)	17.7 (12.6)	.441
BSA (%)	Mean (SD)	21.2 (14.0)	20.0 (12.4)	22.5 (15.6)	.366
PASI score (0-72)	Mean (SD)	16.4 (5.0)	16.2 (4.1)	16.6 (5.9)	.721

- Study 2: Study 2 was the Phase 3 clinical study, CNTO1959PSO3003 (see Section C1.2 above).

Due to a short follow-up period (14 days) and small sample size (n =106) in Study 1, additional validation analyses were conducted (to establish response criteria for use in clinical studies) using data from the open-label period in Study CNTO1959PSO3003 to further assess and support the measurement properties of the PSSD-7 day scale. The demographic and clinical characteristics of the Study 2 participants are shown below:

Study 2 Demographic and Clinical Characteristics

Characteristic	N	871
Age (years):	Mean (SD)	43.1 (13.21)
Sex	Male	566 (65.0%)
	Female	305 (35.0%)
Race	White	747 (85.8%)
	Black or African American	13 (1.5%)
	Asian	103 (11.8%)
Psoriasis disease duration (yrs)	Mean (SD)	16.76 (12.197)
BSA (%)	Mean (SD)	28.2 (16.76)
PASI score (0-72)	Mean (SD)	21.6 (9.24)

Item Analysis and Scaling

Floor and ceiling effects:

In Study 1, item-level descriptive statistics and multi-level exploratory factor analysis (EFA) was used to understand the item level performance and factor structure of the PSSD-7 day and PSSD-24 hour scales. Descriptive information is provided in the tables below. A cut-off of >25% was used to indicate floor/ceiling effects. Significant floor effects were noted for four items of the

Clinical Outcome Assessment Review

Yasmin Choudhry, M.D.

BLA 761061

Guselkumab

Psoriasis Symptoms and Signs Diary (symptom and sign severity)

PSSD-24h, including bleeding (42%), burning (31%), stinging (26%), and pain (26%), while only bleeding (36.2%) evidenced floor effects in the PSSD-7 day scale.

PSSD-24h Severity Item Characteristics Week 1

Item	N	Mean	SD	Floor (n, %)	Ceiling (n, %)	Skew (SE)
Itch	380	4.9	2.7	21 (5.5)	13 (3.4)	-0.14 (0.13)
Dryness	380	5.3	2.9	17 (4.5)	25 (6.6)	-0.17 (0.13)
Cracking	379	4.3	3.0	59 (15.6)	8 (2.1)	0.06 (0.13)
Skin tightness	379	4.0	3.0	55 (14.5)	8 (2.1)	0.27 (0.13)
Scaling	380	5.1	2.9	24 (6.3)	20 (5.3)	-0.17 (0.13)
Flaking	380	5.3	3.0	33 (8.7)	19 (5.0)	-0.29 (0.13)
Redness	379	5.0	3.0	29 (7.7)	13 (3.4)	-0.14 (0.13)
Bleeding	380	2.3	2.8	160 (42.1)	2 (0.5)	1.02 (0.13)
Burning	380	3.3	3.2	119 (31.3)	9 (2.4)	0.49 (0.13)
Stinging	380	3.4	3.0	99 (26.1)	9 (2.4)	0.52 (0.13)
Pain	380	3.5	3.0	97 (25.5)	9 (2.4)	0.48 (0.13)

PSSD-7d Severity Item Characteristics Week 1

Item	N	Mean	SD	Floor (n, %)	Ceiling (n, %)	Skew (SE)
Itch	105	5.4	2.9	4 (3.8)	5 (4.8)	-0.21 (0.24)
Dryness	105	5.9	2.8	2 (1.9)	8 (7.6)	-0.35 (0.24)
Cracking	105	4.8	3.1	9 (8.6)	4 (3.8)	-0.05 (0.24)
Skin tightness	105	4.7	3.0	7 (6.7)	3 (2.9)	0.10 (0.24)
Scaling	105	5.8	3.0	5 (4.8)	8 (7.6)	-0.41 (0.24)
Flaking	105	6.1	2.8	4 (3.8)	8 (7.6)	-0.56 (0.24)
Redness	105	5.7	2.9	5 (4.8)	9 (8.6)	-0.36 (0.24)
Bleeding	105	2.9	3.1	38 (36.2)	3 (2.9)	0.79 (0.24)
Burning	105	3.9	3.3	26 (24.8)	5 (4.8)	0.34 (0.24)
Stinging	105	3.8	3.2	22 (21.0)	3 (2.9)	0.39 (0.24)
Pain	105	4.1	3.3	18 (17.1)	7 (6.7)	0.34 (0.24)

Reviewer comment: *The observed floor effects indicate that some of the items were not relevant to, or experienced by, the patients. The floor effects indicate that a significant proportion of the patients are not experiencing those particular psoriasis signs and symptoms, therefore, would not be able to show improvement on those signs and symptoms in this particular study. These items could have potentially been dropped from the PSSD instrument; however, the Applicant did not make any modification to the PSSD items based on these floor effects. Qualitative data does support retaining burning, stinging, and pain.*

Clinical Outcome Assessment Review

Yasmin Choudhry, M.D.

BLA 761061

Guselkumab

Psoriasis Symptoms and Signs Diary (symptom and sign severity)

Reliability

Internal consistency:

Internal consistency reliability is a measure of how well the items comprising an instrument measure the same general concept.

In Study 1, internal consistency reliability for the PSSD-24 hour scale was evaluated by calculating Cronbach's alpha coefficient for the separate summary scores at Week 1, and by averaging items separately across the 7-day period. Results demonstrated moderate to high internal consistency (alpha = 0.954 to 0.960); alpha coefficient of ≥ 0.70 was considered to represent acceptable reliability.

For the PSSD-7 day scale, internal consistency reliability was evaluated by calculating a Cronbach's alpha coefficient for both scales (signs and symptoms) at Day 7. Results demonstrated alpha = 0.944 to 0.949 (high internal consistency).

The table below shows inter-item correlations between the PSSD 7d severity items at Week 1:

Inter-item Correlations between PSSD-7d Severity Items at Week 1 (N = 105)

	Itch	Dryness	Cracking	Skin tightness	Scaling	Flaking	Redness	Bleeding	Burning	Stinging
Dryness	.775									
Cracking	.771	.792								
Skin tightness	.778	.780	.868							
Scaling	.728	.849	.778	.725						
Flaking	.820	.863	.785	.780	.894					
Redness	.705	.822	.781	.739	.758	.760				
Bleeding	.660	.560	.695	.641	.587	.565	.625			
Burning	.751	.700	.752	.726	.632	.676	.710	.758		
Stinging	.740	.630	.711	.705	.666	.676	.688	.763	.906	
Pain	.795	.696	.816	.771	.685	.702	.693	.722	.877	.823

All correlations significant at $p < .001$

Reviewer comments: *Inter-item correlations >0.80 indicate that there may be some measurement redundancy (e.g., stinging and burning [$r=0.906$]; pain and burning [$r=0.877$]; flaking and scaling [$r=0.894$]; pain and cracking [$r=0.816$]; skin tightness and cracking [$r=0.868$]; scaling and dryness [$r=0.849$]; flaking and itch [0.820]; redness and dryness [0.822]). However, these results are from the PSSD 7-day version. The qualitative data (patient transcripts) support that patients consider these as distinct concepts.*

Test-retest reliability:

The test-retest of an instrument measures the stability of scores over time when no change has occurred in the patient's disease status. In Study 1, test-retest reliability was evaluated for the

Clinical Outcome Assessment Review

Yasmin Choudhry, M.D.

BLA 761061

Guselkumab

Psoriasis Symptoms and Signs Diary (symptom and sign severity)

PSSD-24 hour scale summary and item scale scores by calculating the intraclass correlation coefficient (ICC) using scores at Week 1 and Week 2. Participants who had not changed in severity since baseline on the PGI were included in this analysis. The ICCs for the PSSD-24 hour scale ranged from 0.759 to 0.977 indicating good to excellent test-retest reliability. Similar results were observed for the PSSD-7 day scale.

Test-Retest Reliability Coefficients for the PSSD-24h and PSSD-7d Scores

Summary Score/Item	PSSD-24h	PSSD-7d
	Test-Retest (no change PGI Day 7 to Day 14) ICC (n=24)	Test-Retest (no change PGI Day 7 to Day 14) ICC (n=52)
Symptom Severity	0.952	0.945
Itch	0.955	0.932
Skin Tightness	0.972	0.891
Burning	0.869	0.877
Stinging	0.867	0.892
Pain	0.977	0.880
Signs Severity	0.886	0.894
Dryness	0.919	0.881
Cracking	0.941	0.844
Scaling	0.929	0.896
Shedding/Flaking	0.807	0.785
Redness	0.815	0.845
Bleeding	0.759	0.882

Reviewer comment: *The Applicant has demonstrated that both PSSD versions (24 hour and 7-Day) have acceptable internal consistency and test-retest reliability. However, it remains unclear why some items with high floor effects were retained in the PSSD*

Construct Validity

Convergent and Discriminant Validity:

Convergent and discriminant validity measures the relationships among items, domains, and concepts conform to *a priori* hypotheses concerning logical relationships that should exist with measures of related concepts or scores produced in similar or diverse patient group. Validity is concluded when the associations between concepts measured by a specified instrument and concepts measured by other instruments are as expected.

Construct validity of the PSSD-24 hour scale was evaluated in Study 1 and construct validity of the PSSD-7 day scale was evaluated in Study 2 using the SF-36 and DLQI instruments.

In Study 1, moderate to large correlations were observed with the PSSD-24 hour scale summary scores and the collateral measures:

- Correlation with the DLQI was 0.489 (Symptom Severity)
- Correlation with SF-36 PCS was 0.437 (Symptom Severity)

Clinical Outcome Assessment Review

Yasmin Choudhry, M.D.

BLA 761061

Guselkumab

Psoriasis Symptoms and Signs Diary (symptom and sign severity)

Reviewer comment: A minimum correlation of 0.30 (effect size as defined by Cohen, 1988: Small <0.2; medium 0.2-0.5; large 0.5-0.8) between conceptually similar scales was required for evidence of convergent validity. The PSSD's convergent validity results fall within this pre-defined range. The Pain Severity item demonstrated the strongest correlations with the collateral measures.

Known-Groups Validity:

Analyses of known-groups validity assesses the extent to which a measure's scores are linked to variance in individuals' known health states and characterizes the degree to which scores produced by a target questionnaire can distinguish among groups hypothesized *a priori* to be clinically distinct.

In Study 1, known-groups validity for the PSSD-24 hour scale summary/item scale scores was evaluated by categorizing patients on the basis of baseline PASI ratings (<13, 13–16.9, 17+), Day 7 DLQI scores (<6, 7–15, >16), and baseline PGI rating. The results for the PSSD-24 hour / PSSD-7 day scales demonstrated that there was a trend for numerical differences between groups in mean scores for both scales, as expected, shown consistently across assessments using the PASI, DLQI, and PGI. However, due to small sample sizes, statistically significant differences between groups were only found for some comparisons. See tables 19-24 in the Evidence Dossier.

In Study 2, known groups validity for the PSSD-7 day scale was evaluated by DLQI score at Week 16 (Study 2); PASI score at Week 16 (Study 2); and by IGA score at Week 16 (Study 2). Statistically significant results were observed with all PSSD-7d domains and items with these anchors. See tables 25-27 in the Evidence Dossier.

Reviewer comment: Known groups validity could not be adequately assessed in Study 1 due to small sample sizes. For Study 2, the PSSD-7 day scale known groups validity results appears reasonable. However, it is not clear how the Applicant determined the numerical cutoffs for DLQI, PASI, and PGI for the analyses. Note, the numerical cutoffs are different between Studies 1 and 2.

Ability to detect change:

Ability to detect change measures how well an instrument can identify differences in scores over time in individuals or groups who have changed with respect to the concept.

In Study 1, an anchor scale (i.e., PGI) was used to create responder groups, or improvement categories of patients in order to evaluate the ability of the PSSD-24 hour and PSSD-7 day scale summary and item scale scores to detect change over time. This analysis evaluated how the PSSD scores relate to actual change in patient's symptom severity status and was performed by categorizing patients as responders based on three anchor scales (see adapted tables from the Evidence Dossier below).

Clinical Outcome Assessment Review

Yasmin Choudhry, M.D.

BLA 761061

Guselkumab

Psoriasis Symptoms and Signs Diary (symptom and sign severity)

Study 1: PSSD-24h Scores Ability to Detect Change Using PGI Rating

PSSD-24h Score/PGI rating	N	Standardized Effect Size	Standardized Response Mean	Responsiveness Statistic
Symptom Severity				
Improved	5	-0.211	-0.283	-0.315
Unchanged	38	-0.108	-0.239	-0.230
Worse	11	0.153	0.612	0.374
Overall	54	-0.053	0.126	-0.183

Study 1: PSSD-7d Scores Ability to Detect Change Using PGI Rating

PSSD-24h Score/PGI rating	N	Standardized Effect Size	Standardized Response Mean	Responsiveness Statistic
Symptom Severity				
Improved	14	-0.008	-0.020	-0.020
Unchanged	72	0.179	0.573	0.511
Worse	17	-0.017	-0.041	-0.051
Overall	103	-0.354	-0.735	-0.840

Reviewer comments:

For the PSSD-24 hour scale the standardized effect size (SES) and the standardized response mean (SRM) were calculated as the difference in means between Week 1 and Week 2 scores divided by the Week 1 standard deviation.

The responsiveness statistic was calculated as the difference in means between Week 1 and Week 2 scores divided by the standard deviation of the change score for stable patients (defined as those who rated themselves as unchanged on the PGI at Day 14). Responsiveness information was reported for the overall sample as well as separately by PGI group. In addition, mean change scores was calculated, by percent change in PASI group (very much improved = $\geq 50\%$; improved = 1 to 49%; no change = 0%; worse = $> 0\%$ to $\geq 1\%$ worse).

For the PSSD-7 day scale, parallel analyses were calculated using Day 7 and Day 14 scores. However, due to the short time period between these assessment points, these results were exploratory.

Clinical Outcome Assessment Review

Yasmin Choudhry, M.D.

BLA 761061

Guselkumab

Psoriasis Symptoms and Signs Diary (symptom and sign severity)

The data from these analyses should be interpreted cautiously as the changes seen in the PSSD-24 hour scale was numerically small for both improvement and worsening categories. Additionally, there were minimal patients who were categorized as improved. Statistical significance was not evaluated.

In Study 2, the ability of the PSSD-7 day scale to detect change was assessed with patients categorized on the basis of DLQI (0–1, 2–5, 6–10, 11–20, >20), PASI (0–1, 1–9, 10–12, >12) and IGA (0, 1, 2, 3, 4) scores at Week 16.

Reviewer comments: *The SES was calculated as the change in PSSD scores divided by the standard deviation of the baseline for each subgroup.*

Results demonstrated statistically significant greater mean decreases on both PSSD-7 day scale summary scores with all anchors (see adapted tables from the Evidence Dossier below). Similar findings were evidenced for the individual items as well (see full version of Tables 30-32 in the Evidence Dossier).

Study 2: PSSD-7d Scores Ability to Detect Change Using DLQI

PSSD-7d	Improvement in DLQI Score at Week 16				
	No change or worsening (N= 50)	1-4 (N= 125)	5-10 (N= 258)	>10 (N= 415)	p- value
Symptom score	3.4 (20.05); 0.12	-17.3 (18.5); - 0.76	-30.6 (21.35); - -1.3	-50.7 (22.4); - 2.33	<0.0001

Study 2: PSSD-7d Scores Ability to Detect Change Using PASI

PSSD-7d	Improvement in PASI Score at Week 16					p- value
	No change or worsening (N= 14)	0 - <50 (N= 125)	50 - <75 (N= 258)	75 - <90 (N= 415)	≥90	
Symptom score	6.3 (19.95); 0.28	-16.5 (23.49); - 0.64	-31.5 (24.11); - 1.23	-38.2 (25.54); - 1.54	-42.7 (25.30); - 1.76	<0.0001

Study 2: PSSD-7d Scores Ability to Detect Change Using IGA

PSSD-7d	Improvement in DLQI Score at Week 16
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Clinical Outcome Assessment Review

Yasmin Choudhry, M.D.

BLA 761061

Guselkumab

Psoriasis Symptoms and Signs Diary (symptom and sign severity)

	No change or worsening (N= 76)	-1 (N= 156)	-2 (N= 341)	-3 or -4 (N= 275)	p- value
Symptom score	-13 (24.59); -0.56	-30 (25.89); -1.12	-39 (24.95); -1.61	-43.3 (25.75); -1.79	<0.0001

Reviewer comments: *Generally, patient global rating anchors are used as anchors. DLQI is not a global rating and may not be a meaningful anchor. It is unclear how the numerical cutoffs in the DLQI were determined and if they correspond to worsening or improvement appropriately. Further, the IGA and PASI are clinician ratings and do not provide the patient perspective; they also cannot assess worsening.*

6 INTERPRETATION OF SCORES

In Study 1, a distribution-based approach was used to estimate the minimal important difference (MID) for each instrument. Due to the fact that this study had a short follow-up period, the anchor-based approach in this study was considered exploratory (and results are not reported in the dossier).

As noted earlier, data from Study 2, the open labeled phase of CNTO1959PSO3003 Phase 3 clinical study were used to develop responder criteria. An anchor-based approach and cumulative distribution function (CDF) plots were used to estimate the responder threshold for the PSSD-7 day scale. An anchor-based approach and CDFs were used to estimate the responder threshold for the PSSD-7 day version, and those findings were applied to the PSSD-24 hour scale based on the evidence supporting equivalence between the two versions.

Distribution-Based Analyses

Standard error of measurement (SEM) values range from 5.7 – 8.5 for PSSD-24h Symptom and Sign scores, and the values for 0.5 Cohen’s *d* range from 12.6 – 13.1. SEM values range from 6.7 – 8.6 for PSSD-7d Symptom and Sign scores, and the values for 0.5 Cohen’s *d* range from 13.1 – 14.3.

Reviewer comments: *The SEM, threshold values of 1 SEM were used to define clinically meaningful differences.*

For PSSD-24 hour scores, the minimal detectable change (MDC) (i.e., The MDC represents the smallest change that can be reliably distinguished from random fluctuation, and thus represents the lower bound for establishing the MID) was established by comparing distribution-based estimates. Anchor-based estimates of the MID range were then compared. A final MID range was established that was greater than the MDC and integrates estimates from the various anchors. The Applicant placed greater emphasis on the SEM to be conservative. Based on the SEM, the MDC values appear to be 8-10 point range for the

Clinical Outcome Assessment Review

Yasmin Choudhry, M.D.

BLA 761061

Guselkumab

Psoriasis Symptoms and Signs Diary (symptom and sign severity)

PSSD-24h Symptom and Sign scores, and 10-12 for the PSSD-7d Symptom and Sign scores. For both instruments, conservative MDC values appear to be 1-point for all individual item scale scores.

Distribution-based methods are viewed as an exploratory method to provide supportive information to the responder threshold (i.e., threshold for meaningful change) obtained from the anchor-based method. Distribution-based methods should not be used as the sole basis for determining the responder threshold.

Anchor-based Analysis for Responder Criteria

IGA was used as the primary anchor (with a cut-off of -2) to determine the clinically meaningful change of the PSSD-7 day scale summary and item scores at Week 16. Improvement of 75% to < 90% in PASI was used as a secondary anchor. See table below.

Anchor-based Analysis for Threshold of Clinical Response in PSSD Scores

PSSD	Participants with IGA Change of -2 (N=342)	Participants with PASI Improvement of 75-<90% (N=214)	Recommended Cut-off for a Clinical Response
Symptom	-39	-44.0	≥40
Itch	-4.4	-4.1	≥4
Skin Tightness	-4.4	-4.2	≥4
Burning	-3.9	-3.9	≥4
Stinging	-3	-3.0	≥3
Pain	-3.9	-3.8	≥4
Sign	-44	-38.2	≥40
Dryness	-4.6	-4.3	≥4
Cracking	-4.2	-4.3	≥4
Scaling	-5	-4.8	≥5
Shedding or Flaking	-5.3	-5.1	≥5
Redness	-5	-4.9	≥5
Bleeding	-2.6	-2.9	≥3

The following thresholds were considered as clinically meaningful improvement:

- A change of ≥40 points (on a 0-100 scale) from baseline for each of the PSSD-7d Symptom and Sign scale summary scores.
- For the individual items (on a 0-10 scale):
 - A change of ≥3 points from baseline for Bleeding and Stinging items

Clinical Outcome Assessment Review

Yasmin Choudhry, M.D.

BLA 761061

Guselkumab

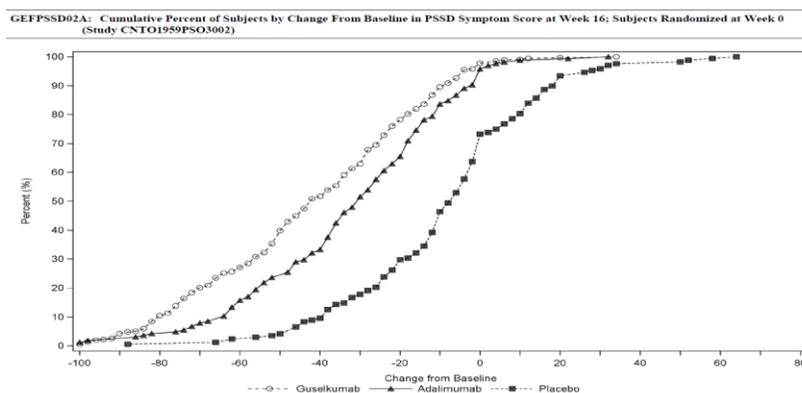
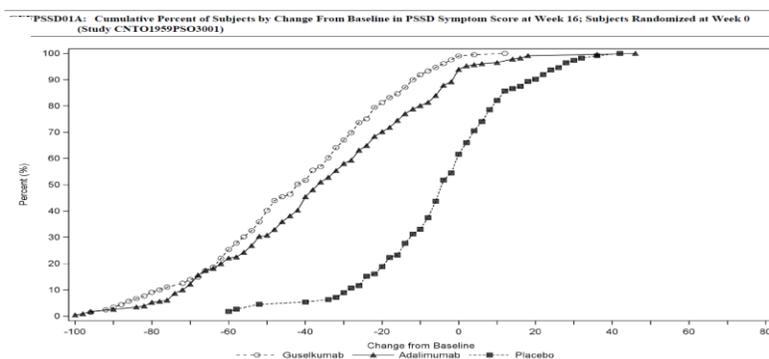
Psoriasis Symptoms and Signs Diary (symptom and sign severity)

- A change of ≥ 4 points from baseline for Itch, Dryness, Cracking, Skin Tightness, Burning, and Pain items,
- A change of ≥ 5 points for Scaling, Shedding or Flaking, and Redness items.

Reviewer comments: *The Applicant concludes that these clinically meaningful response thresholds are supported by the anchor-based analyses, and represent larger magnitudes of change than identified using the distribution based methods. As noted before, generally, patient global rating anchors are used as anchors. However, the Applicant also performed a pre-specified analysis evaluating the proportion of patients achieving a “0” on the PSSD Symptom scores. This analysis can provide meaningful information as it is indicating complete clearance of symptoms and improves data interpretability with the use of the transformed scores.*

Cumulative distribution function curves

The CDFs were plotted using data from the two phase 3 clinical studies, CNTO1959PSO3001 and CNTO1959PSO3002. CDFs of change in the PSSD-24 hour scale summary and item scores at Week 16 by treatment arm (placebo, guselkumab and adalimumab). The change in the PSSD symptom scores are plotted on the x-axis. The y-axis represents the cumulative percentages of the patients having a particular change in the PSSD symptom score (from the x-axis).



Clinical Outcome Assessment Review

Yasmin Choudhry, M.D.

BLA 761061

Guselkumab

Psoriasis Symptoms and Signs Diary (symptom and sign severity)

Reviewer comments: The CDF plots show a clear separation between the treatment arms and the placebo arm at a score change of 40 points. These findings support the applicant's proposed threshold for meaningful change derived from the anchor-based analyses for the PSSD-7 day version. Note that there is not a wide separation between both the treatment arms (Guselkumab and Adalimumab).

Equivalence of the PSSD-24 hour and 7 day scale scores:

In Study 1, correlations were found to be high between both the PSSD-24h and PSSD-7d scales at Week 1 (Day 7) for the Symptom score ($r= 0.95$) and Sign score ($r= 0.95$). For the item level analyses, correlations between the two versions ranged from 0.90 to 0.95.

Reviewer comments: Initially, the Applicant only provided Pearson correlations between the PSSD-24 hour scale (Week 1) and PSSD-7 day version (Day 7) scores to assess equivalence between the two versions of the instrument. In response to FDA information request (IR), the Applicant provided correlations for the PSSD-24 hour scale at Week 2 and the PSSD-7 day scale at Day 14 ($r= 0.97$). Refer to the Sponsor's Response to IR (SDN 16) received February 21, 2017. Based on the data generated from the psychometric analyses, the PSSD-24 hour and 7 day scales appear to perform similarly. The responder threshold derived from the PSSD-7 day scale seems to provide a clear separation between the treatment and placebo arms based on the CDF plots using the PSSD-24 hour scale.

7 LANGUAGE TRANSLATION AND CULTURAL ADAPTATION

The PSSD-24 hour scale was translated in to the following languages: Australia-English, Canada-English, Canada-French, Czech Republic-Czech, Germany-German, UK-English, Hungary-Hungarian, Poland-Polish, Russia-Russian, South Korea-Korean, Spain-Spanish, Taiwan-Chinese, and USA-Spanish. The methodology used for the development of each language version of the PSSD was in line with the ISPOR Task Force recommendations (Wild et al., 2005) and included two forward translations, two back translations, cognitive debriefing and proofreading.

Reviewer comments: The methodology used for the development of each language version of the PSSD was in line with the ISPOR Task Force recommendations (Wild et al., 2005) and included two forward translations, two back translations, cognitive debriefing and proofreading.

8 REFORMATTING FOR NEW METHOD OR MODE OF ADMINISTRATION

The PSSD is available in both, paper and electronic modes.

Clinical Outcome Assessment Review

Yasmin Choudhry, M.D.

BLA 761061

Guselkumab

Psoriasis Symptoms and Signs Diary (symptom and sign severity)

The Applicant conducted a study (n=14; adults with mild, moderate and severe psoriasis) to assess the content equivalence between the paper-and-pencil and electronic versions of the PSSD and to assess the usability of the electronic versions of the PSSD on the LogPad® (24-hour recall) and SitePad® (7-day recall) in patients with clinician-confirmed plaque psoriasis. Two rounds of interviews were conducted:

LogPad® (24-hour recall):

Participants in Round 1 provided recommendations for changes to this device (such as increasing the font size on the NRS, question wording and instructions). Some participants (n=4, 57%) indicated they were not able to easily select their intended response when completing the PSSD on the device because the size of the response scale was too small and they inadvertently selected a different number with their finger. These participants noted they did not try to correct their response on the NRS because it appeared to be similar or within the same “range” as their intended response.

Based on the feedback from Round 1, the font size for the instructions, question wording and NRS were increased; and additional training was added for Round 2 to show participants how to change their answers and navigate between screens. Participants were also trained how to use the stylus to complete the PSSD on the LogPad® in the event the stylus was more sensitive to the touchscreen versus their finger.

In Round 2, three participants (43%) suggested improvements to this device. Similar to Round 1, their suggestions included increasing the font size of the NRS (n=1), the font size of the question wording or instructions (n=2), and having difficulty selecting the intended answer (n=1).

SitePad® (7-day recall):

Most participants in Round 1 (n=6, 86%) suggested improvements to this device: Six (86%) participants commented that the device seemed “bulky” or “heavy”; two reported the screen “dimmed” while they were reviewing the screens; three (43%) recommended increasing the font size of the question wording, instructions, and NRS; two participants suggested changing the response scale so their selected answers would become “highlighted” in orange similar to the NRS on the LogPad®.

Based on feedback in Round 1, participants in Round 2 were trained how to use the stand on the SitePad® and the dim timeout period was increased. Additional instructions were provided during the training to show participants how to change the screen back to normal viewing if the device dimmed. In Round 2, a few participants (n=3, 43%) recommended improvements to the SitePad®. Similar to Round 1, three participants (43%) suggested increasing the font size to the question wording (n=2) or NRS (n=2). The font size was not increased due to space constraints of other instruments being used on the SitePad® device in the study. No participants in Round 2 reported any issues with the weight of the device.

Clinical Outcome Assessment Review

Yasmin Choudhry, M.D.

BLA 761061

Guselkumab

Psoriasis Symptoms and Signs Diary (symptom and sign severity)

9 REVIEW USER MANUAL

The Applicant submitted a (brief) PSSD user manual which included instructions for administration of the PSSD, administration timing, method (e.g., paper or pencil, electronic), and mode (e.g., self-, clinician-, or interviewer-administered), and scoring algorithm/score interpretation.

10 KEY REFERENCES FOR MEASURE

11 APPENDICES

Clinical Outcome Assessment Review

Yasmin Choudhry, M.D.

BLA 761061

Guselkumab

Psoriasis Symptoms and Signs Diary (symptom and sign severity)

Appendix A Psoriasis symptom and Signs Diary (PSSD)-24h (Paper version)

Psoriasis Symptom Diary

Please answer each question to the best of your ability. There are no right or wrong answers. Please pay close attention to the time period of interest. These questions ask you to think about the **past 24 hours**. **Please complete the diary at the same time every day.** Individuals with psoriasis may experience a range of symptoms. Please indicate how severe each of the following skin symptoms was in the **past 24 hours**. Please select only one number for each item on the 0 to 10 scale (0=Absent and 10= Worst imaginable).

1. Rate the severity of <u>itch</u> in the past 24 hours.	0 Absent	1	2	3	4	5	6	7	8	9	10 Worst Imaginable
2. Rate the severity of <u>dryness</u> in the past 24 hours.	0 Absent	1	2	3	4	5	6	7	8	9	10 Worst Imaginable
3. Rate the severity of <u>cracking</u> in the past 24 hours.	0 Absent	1	2	3	4	5	6	7	8	9	10 Worst Imaginable
4. Rate the severity of <u>skin tightness</u> in the past 24 hours.	0 Absent	1	2	3	4	5	6	7	8	9	10 Worst Imaginable
5. Rate the severity of <u>scaling (build-up of skin)</u> in the past 24 hours.	0 Absent	1	2	3	4	5	6	7	8	9	10 Worst Imaginable
6. Rate the severity of <u>shedding or flaking</u> in the past 24 hours.	0 Absent	1	2	3	4	5	6	7	8	9	10 Worst Imaginable
7. Rate the severity of <u>redness</u> in the past 24 hours.	0 Absent	1	2	3	4	5	6	7	8	9	10 Worst Imaginable
8. Rate the severity of <u>bleeding</u> in the past 24 hours.	0 Absent	1	2	3	4	5	6	7	8	9	10 Worst Imaginable
9. Rate the severity of <u>burning</u> in the past 24 hours.	0 Absent	1	2	3	4	5	6	7	8	9	10 Worst Imaginable
10. Rate the severity of <u>stinging</u> in the past 24 hours.	0 Absent	1	2	3	4	5	6	7	8	9	10 Worst Imaginable
11. Rate the severity of <u>pain from your psoriasis lesions</u> in the past 24 hours.	0 Absent	1	2	3	4	5	6	7	8	9	10 Worst Imaginable

Clinical Outcome Assessment Review

Yasmin Choudhry, M.D.

BLA 761061

Guselkumab

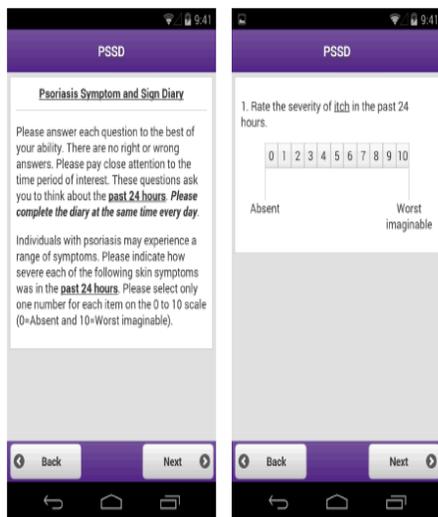
Psoriasis Symptoms and Signs Diary (symptom and sign severity)

Appendix B Psoriasis Symptom and Sign Diary (PSSD)-24h (Electronic snap shots)

Appendix N1. LogPad (eDiary) Version of the PSSD-24h

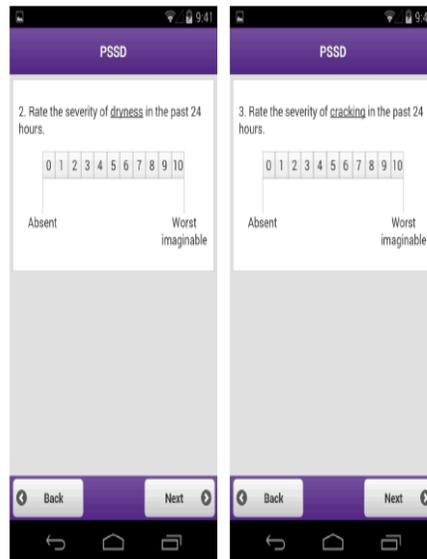
LogPad (eDiary) Version of the PSSD-24h (b) (4)

LogPad® (eDiary) Version of the PSSD-24h

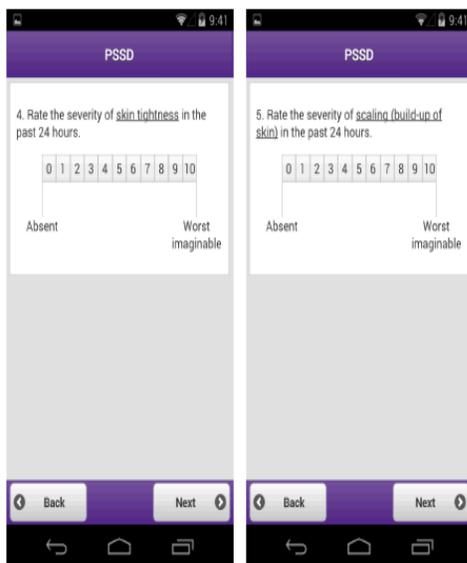


Appendix N1. LogPad (eDiary) Version of the PSSD-24h

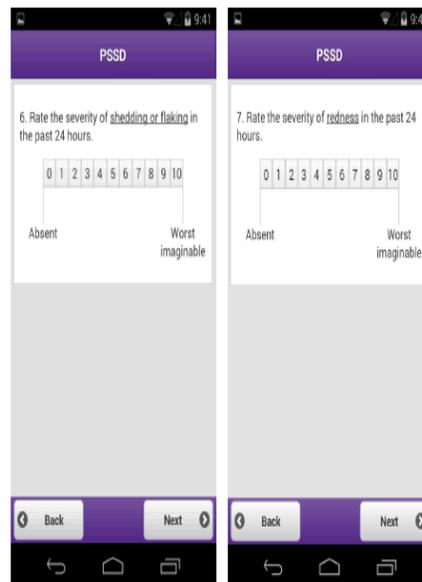
LogPad (eDiary) Version of the PSSD-24h (b) (4)



LogPad (eDiary) Version of the PSSD-24h (b) (4)



LogPad (eDiary) Version of the PSSD-24h (b) (4)



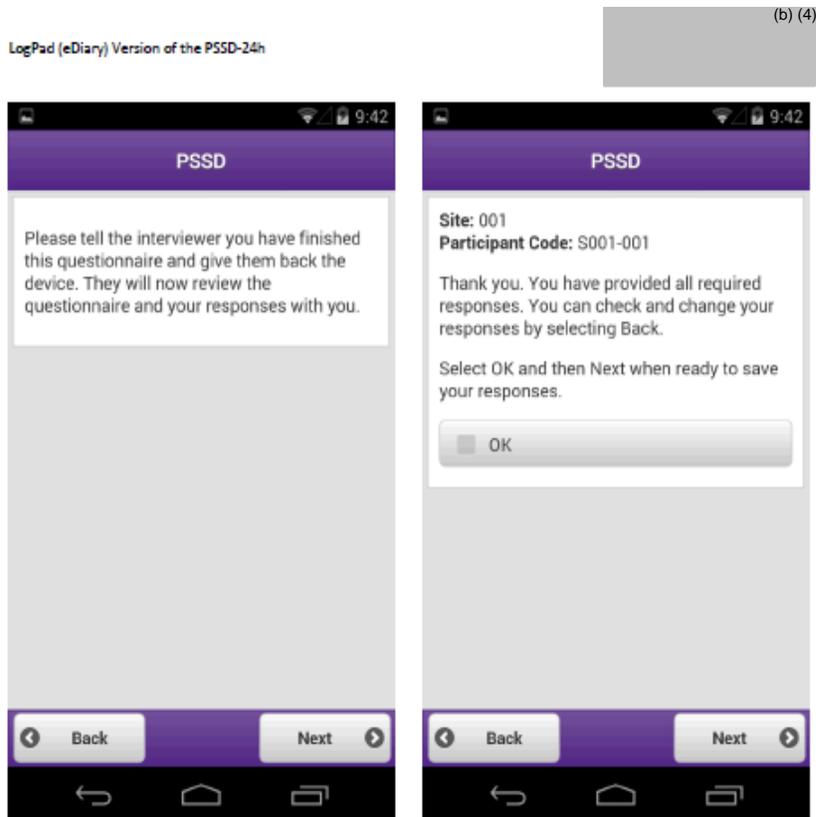
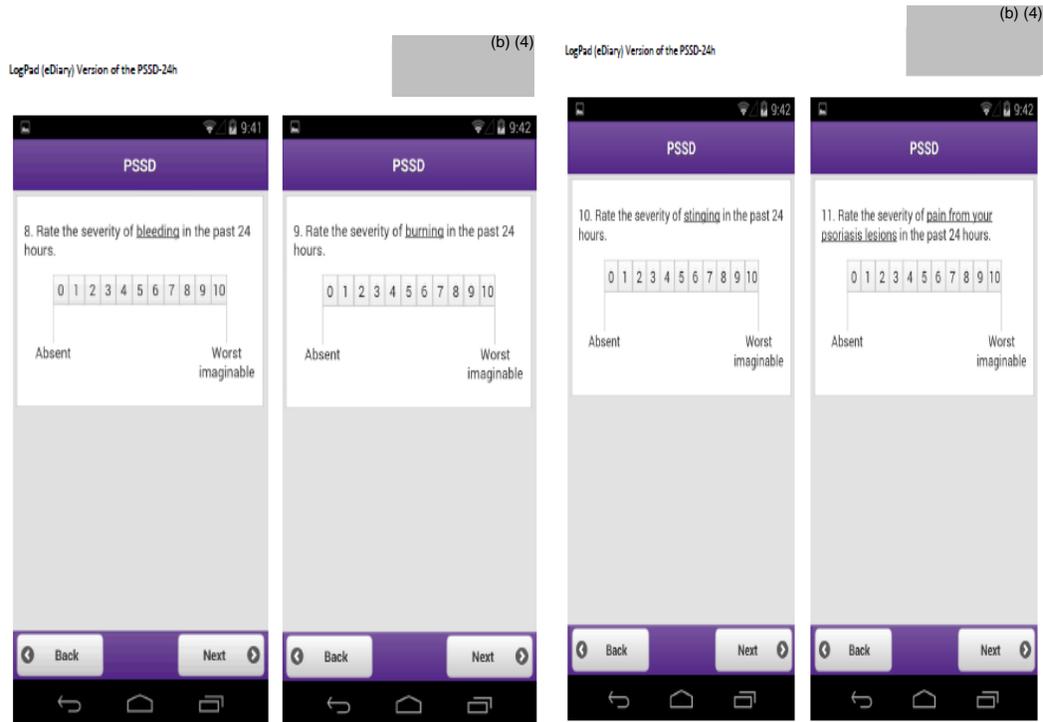
Clinical Outcome Assessment Review

Yasmin Choudhry, M.D.

BLA 761061

Guselkumab

Psoriasis Symptoms and Signs Diary (symptom and sign severity)



Clinical Outcome Assessment Review

Yasmin Choudhry, M.D.

BLA 761061

Guselkumab

Psoriasis Symptoms and Signs Diary (symptom and sign severity)

Appendix C Psoriasis Symptom and Sign Diary (PSSD)-7d (Electronic screenshots)

Janssen Subject: ZZ99999-X0001 PSSD
CNT01959P50300X[T] V1.22 Site: ZZ99999 Logged In As: (b) (6) 1/12 10:00 A.M.

Psoriasis Symptom and Sign Diary

Please answer each question to the best of your ability. There are no right or wrong answers. Please pay close attention to the time period of interest. These questions ask you to think about the past 7 days.

Individuals with psoriasis may experience a range of symptoms. Please indicate how severe each of the following skin symptoms was in the past 7 days. Please select only one number for each item on the 0 to 10 scale (0=Absent and 10=Worst imaginable).

Back **Next**

Janssen Subject: ZZ99999-X0001 PSSD
CNT01959P50300X[T] V1.22 Site: ZZ99999 Logged In As: (b) (6) 2/12 10:00 A.M.

1. Rate the severity of itch in the past 7 days.

0 1 2 3 4 5 6 7 8 9 10
Absent Worst imaginable

Back **Next**

Clinical Outcome Assessment Review

Yasmin Choudhry, M.D.

BLA 761061

Guselkumab

Psoriasis Symptoms and Signs Diary (symptom and sign severity)

Janssen Subject: Z79999-X0001 PSSD
CNT01959PS0300X[T] V1.22 Site: Z299999 Logged In As: (b) (6) 3/12 10:00 A.M.

2. Rate the severity of dryness in the past 7 days.

0 1 2 3 4 5 6 7 8 9 10
Absent Worst imaginable

Back Next

Janssen Subject: Z79999-X0001 PSSD
CNT01959PS0300X[T] V1.22 Site: Z299999 Logged In As: (b) (6) 4/12 10:00 A.M.

3. Rate the severity of cracking in the past 7 days.

0 1 2 3 4 5 6 7 8 9 10
Absent Worst imaginable

Back Next

Clinical Outcome Assessment Review

Yasmin Choudhry, M.D.

BLA 761061

Guselkumab

Psoriasis Symptoms and Signs Diary (symptom and sign severity)

Janssen Subject: Z79999-X0001 PSSD
CNT01959#PS0300X[T] V1.22 Site: Z79999 Logged In As: (b) (6) 5/12 10:00 A.M.

4. Rate the severity of skin tightness in the past 7 days.

0 1 2 3 4 5 6 7 8 9 10
Absent Worst imaginable

Back Next

Janssen Subject: Z79999-X0001 PSSD
CNT01959#PS0300X[T] V1.22 Site: Z79999 Logged In As: (b) (6) 6/12 10:00 A.M.

5. Rate the severity of scaling (build-up of skin) in the past 7 days.

0 1 2 3 4 5 6 7 8 9 10
Absent Worst imaginable

Back Next

Clinical Outcome Assessment Review

Yasmin Choudhry, M.D.

BLA 761061

Guselkumab

Psoriasis Symptoms and Signs Diary (symptom and sign severity)

Janssen Subject: ZZ9999-X0001 PSSD
CNT01959F50300X[T] V1.22 Site: ZZ99999 Logged In As: (b) (6) 7/12 10:00 A.M.

6. Rate the severity of shedding or flaking in the past 7 days.

0 1 2 3 4 5 6 7 8 9 10
Absent Worst imaginable

Back Next

Janssen Subject: ZZ9999-X0001 PSSD
CNT01959F50300X[T] V1.22 Site: ZZ99999 Logged In As: (b) (6) 8/12 10:00 A.M.

7. Rate the severity of redness in the past 7 days.

0 1 2 3 4 5 6 7 8 9 10
Absent Worst imaginable

Back Next

Clinical Outcome Assessment Review

Yasmin Choudhry, M.D.

BLA 761061

Guselkumab

Psoriasis Symptoms and Signs Diary (symptom and sign severity)

Janssen Subject: ZZ99999-X0001 PSSD
CNT01959PS0300X[TJ] V1.22 Site: ZZ99999 Logged In As: (b) (6) 9/12 10:00 A.M.

8. Rate the severity of bleeding in the past 7 days.

0	1	2	3	4	5	6	7	8	9	10
---	---	---	---	---	---	---	---	---	---	----

Absent Worst imaginable

Back Next

Janssen Subject: ZZ99999-X0001 PSSD
CNT01959PS0300X[TJ] V1.22 Site: ZZ99999 Logged In As: (b) (6) 10/12 10:00 A.M.

9. Rate the severity of burning in the past 7 days.

0	1	2	3	4	5	6	7	8	9	10
---	---	---	---	---	---	---	---	---	---	----

Absent Worst imaginable

Back Next

Clinical Outcome Assessment Review

Yasmin Choudhry, M.D.

BLA 761061

Guselkumab

Psoriasis Symptoms and Signs Diary (symptom and sign severity)

Janssen Subject: ZZ99999-X0001 PSSD
CNT01959PS0300X[T] V1.22 Site: ZZ99999 Logged In As (b) (6) 11/12 10:00 A.M.

10. Rate the severity of stinging in the past 7 days.

0	1	2	3	4	5	6	7	8	9	10
---	---	---	---	---	---	---	---	---	---	----

Absent Worst imaginable

Back Next

Janssen Subject: ZZ99999-X0001 PSSD
CNT01959PS0300X[T] V1.22 Site: ZZ99999 Logged In As (b) (6) 12/12 10:00 A.M.

11. Rate the severity of pain from your psoriasis lesions in the past 7 days.

0	1	2	3	4	5	6	7	8	9	10
---	---	---	---	---	---	---	---	---	---	----

Absent Worst imaginable

Back Next

Clinical Outcome Assessment Review

Yasmin Choudhry, M.D.

BLA 761061

Guselkumab

Psoriasis Symptoms and Signs Diary (symptom and sign severity)

Janssen Subject: ZZ99999-X0001 PSSD
ONT01959F50300X[T] V1.22 Site: ZZ99999 Logged In As (b) (6) 10:00 A.M.

I hereby state that I have answered all questions to the best of my ability.

[Back](#) [Finish](#)

Clinical Outcome Assessment Review

Yasmin Choudhry, M.D.

BLA 761061

Guselkumab

Psoriasis Symptoms and Signs Diary (symptom and sign severity)

Psoriasis Symptom Diary

Please answer each question to the best of your ability. There are no right or wrong answers. Please pay close attention to the time period of interest. These questions ask you to think about the past 7 days.

1. Individuals with psoriasis may experience a range of symptoms. Please indicate how severe each of the following skin symptoms was in the past 7 days. Please select only one number for each item on the 0 to 10 scale (0=Absent and 10= Worst imaginable).

1. Rate the severity of <u>itch</u> in the past 7 days.	0 Absent	1	2	3	4	5	6	7	8	9	10 Worst imaginable
2. Rate the severity of <u>dryness</u> in the past 7 days.	0 Absent	1	2	3	4	5	6	7	8	9	10 Worst imaginable
3. Rate the severity of <u>cracking</u> in the past 7 days.	0 Absent	1	2	3	4	5	6	7	8	9	10 Worst imaginable
4. Rate the severity of <u>skin tightness</u> in the past 7 days.	0 Absent	1	2	3	4	5	6	7	8	9	10 Worst imaginable
5. Rate the severity of <u>scaling (build-up of skin)</u> in the past 7 days.	0 Absent	1	2	3	4	5	6	7	8	9	10 Worst imaginable
6. Rate the severity of <u>shedding or flaking</u> in the past 7 days.	0 Absent	1	2	3	4	5	6	7	8	9	10 Worst imaginable
7. Rate the severity of <u>redness</u> in the past 7 days.	0 Absent	1	2	3	4	5	6	7	8	9	10 Worst imaginable
8. Rate the severity of <u>bleeding</u> in the past 7 days.	0 Absent	1	2	3	4	5	6	7	8	9	10 Worst imaginable
9. Rate the severity of <u>burning</u> in the past 7 days.	0 Absent	1	2	3	4	5	6	7	8	9	10 Worst imaginable
10. Rate the severity of <u>stinging</u> in the past 7 days.	0 Absent	1	2	3	4	5	6	7	8	9	10 Worst imaginable
11. Rate the severity of <u>pain from your psoriasis lesions</u> in the past 7 days.	0 Absent	1	2	3	4	5	6	7	8	9	10 Worst imaginable

Clinical Outcome Assessment Review

Yasmin Choudhry, M.D.

BLA 761061

Guselkumab

Psoriasis Symptoms and Signs Diary (symptom and sign severity)

2. Individuals with psoriasis may experience a range of symptoms. Please answer each question below indicating the number of days you experienced each of the skin symptoms in the **past 7 days**. Please select one response only for each question.

1. On how many of the past 7 days did you experience itch?	None of the days (0 days)	A small number of days (1-2 days)	Some days (3-4 days)	Most days (5-6 days)	All of the days (7 days)
2. On how many of the past 7 days did you experience dryness?	None of the days (0 days)	A small number of days (1-2 days)	Some days (3-4 days)	Most days (5-6 days)	All of the days (7 days)
3. On how many of the past 7 days did you experience cracking?	None of the days (0 days)	A small number of days (1-2 days)	Some days (3-4 days)	Most days (5-6 days)	All of the days (7 days)
4. On how many of the past 7 days did you experience skin tightness?	None of the days (0 days)	A small number of days (1-2 days)	Some days (3-4 days)	Most days (5-6 days)	All of the days (7 days)
5. On how many of the past 7 days did you experience scaling (build-up of skin)?	None of the days (0 days)	A small number of days (1-2 days)	Some days (3-4 days)	Most days (5-6 days)	All of the days (7 days)
6. On how many of the past 7 days did you experience shedding or flaking?	None of the days (0 days)	A small number of days (1-2 days)	Some days (3-4 days)	Most days (5-6 days)	All of the days (7 days)
7. On how many of the past 7 days did you experience redness?	None of the days (0 days)	A small number of days (1-2 days)	Some days (3-4 days)	Most days (5-6 days)	All of the days (7 days)
8. On how many of the past 7 days did you experience bleeding?	None of the days (0 days)	A small number of days (1-2 days)	Some days (3-4 days)	Most days (5-6 days)	All of the days (7 days)
9. On how many of the past 7 days did you experience burning?	None of the days (0 days)	A small number of days (1-2 days)	Some days (3-4 days)	Most days (5-6 days)	All of the days (7 days)
10. On how many of the past 7 days did you experience stinging?	None of the days (0 days)	A small number of days (1-2 days)	Some days (3-4 days)	Most days (5-6 days)	All of the days (7 days)
11. On how many of the past 7 days did you experience pain associated with your psoriasis lesions?	None of the days (0 days)	A small number of days (1-2 days)	Some days (3-4 days)	Most days (5-6 days)	All of the days (7 days)

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

/s/

YASMIN A CHOUDHRY
04/05/2017

SELENA R DANIELS
04/05/2017

ELEKTRA J PAPADOPOULOS
04/08/2017

**GENERAL HOSPITAL DEVICES BRANCH
INTERCENTER CONSULT MEMORANDUM**

Date: March 10, 2017

To: Matthew White, Senior Regulatory Health Project Manager
CDER/OND/ODEIII/DDDP

From: LCDR Keith Marin

Through: CDR Alan Stevens, Branch Chief
General Hospital Devices Branch

Subject: Consult for BLA 761061, ICC1600805

Applicant	Janssen Research & Development, LLC
Indication for Use	Guselkumab is a human interleukin-23 antagonist indicated for the treatment of adult patients with moderate-to-severe plaque psoriasis who are candidates for systemic therapy or phototherapy
Biologic Constituent	Guselkumab
Device Constituent	Pre-filled syringe

Recommendation: Based on information reviewed BLA 761061, the sponsor has provided sufficient information for the pre-filled syringe. All interactive review questions have been satisfactorily addressed, As a result, CDRH/ODE recommends approval for the BLA for this combination product.

Digital Signature Concurrence Table	
Reviewer	Keith G. Marin -A Digitally signed by Keith G. Marin - A DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Keith G. Marin -A, 0.9.2342.19200300.100.1.1=0011250397 Date: 2017.03.20 11:52:22 -04'00'
Branch Chief	Alan M. Stevens -S Alan M. Stevens - S 2017.03.22 07:33:51 -04'00'

I. Purpose / Background

The Center for Drug Evaluation and Research (CDER) has requested a consult from the Center for Devices and Radiological Health (CDRH), regarding a review request for BLA 761061. The device constituent of this combination product consists of a pre-filled syringe designed to deliver Guselkumab, for injection. Guselkumab is a human interleukin-23 antagonist indicated for the treatment of adult patients with moderate-to-severe plaque psoriasis who are candidates for systemic therapy or phototherapy.

The original consult request from CDER indicates that, "Guselkumab is a human interleukin-23 antagonist indicated for the treatment of adult patients with moderate-to-severe plaque psoriasis who are candidates for systemic therapy or phototherapy. The sponsor used a priority review voucher for this BLA. Guselkumab is an 100mg/mL injection supplied in a single-dose prefilled syringe. DDDP requests a CDRH device component evaluation."

The device presentation that is being evaluated within this review is a pre-filled syringe. Device performance will be the focus of this review. Device/drug compatibility will be deferred to CDER.

There is no record of past CDRH interaction related to this combination product.

Reviewer's Note: Reviewer's Note: File was originally assigned to Onwuatuegwu Echezona and later reassigned to me. Review of the information for the filing meeting, the following information could not be found:

- LOA for the K (b) (4) and K (b) (4)
- Essential performance specifications
- Design verification and validation testing of the combination product (I see it for the needlestick feature but not overall such as dose accuracy, breakloose/glide force, etc.)
- Design and lot release specifications for the device (nothing on device in 3.2.P.5.1)
- Risk analysis for final device constituent of combination product
- Biocompatibility testing
- Shipping studies

The sponsor was contacted on January 9, 2017 and this information was requested. On January 23, 2017, the sponsor provided the response to where this information could be found. Adequacy of this information will be a review issue addressed in this memo.

II. Administrative

Documents Reviewed:

Cross-Referenced 510(k) #	Letter of Authorization Included in NDA / BLA	
	YES	NO
(b) (4)	X	
		X

Reviewer's Note: (b) (4)

[Redacted]

As long as the sponsor provides the necessary information for the safety device in the BLA, this should be acceptable.

Document Title	Document Number	Date –Version	Location
Container Closure	3.2.P.7	11/16/2016	GSR Sequence 0000 / Section 3.2.P.7
Specifications	3.2.P.5.1	11/16/2016	GSR Sequence 0000 / 3.2.P.5.1
Stability	3.2.P.8	11/16/2016	GSR Sequence 0000 / 3.2.P.8
Letter of Authorization and Right of Reference	1.4.1	01/23/2017	GSR Sequence 0000 / Section 1.4.1
Analytical Procedures	3.2.P.5.2	11/16/2016	GSR Sequence 0000 / Section 3.2.P.5.2
Medical Device- (b) (4)	3.2.R.2	11/16/2016	GSR Sequence 0000 / Section 3.2.R.2
Shipping studies	3.2.P.3.5	11/16/2016	GSR Sequence 0000 / Section 3.2.P.3.5

CDRH Review Team:

Team Member	Role	Deficiencies
Keith Marin {(CDRH/ODE/GHDB)}	Lead Reviewer – Nurse consultant	None

III. Device Description and Performance Requirements

Indications for Use	
Guselkumab for injection	Guselkumab is indicated for the treatment of adult patients with moderate-to-severe plaque psoriasis who are candidates for systemic therapy or phototherapy.



Table 1: Description of Syringe Barrel with Fixed Needle and RNS

Components	Description	Supplier	DMF
(b) (4)			

Table 2: Critical Dimensions of Syringe Barrel With Fixed Needle and RNS

Description	Dimension (mm)	Tolerances (mm)
(b) (4)		

Table 3: Description of the Plunger Stopper

Components	Description	Supplier	DMF
(b) (4)			

Table 4: Critical Dimensions of the Plunger Stopper

Description	Dimension	Tolerance
(b) (4)		

Reviewer's Note: Compatibility of the plunger stopper with the biologic will be deferred to CDER as the biologic is in direct contact with the plunger stopper. However, based on dimensions of the plunger stopper and barrel of syringe, they appear to be compatible.

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

(b) (4)

Reviewer's Note: The sponsor has stated that they have incorporated elements of Design Controls per 21 CFR 820.30 taking into account user needs, intended uses, safety, efficacy, performance, and reliability. The applicable functional requirements, for example: Seal Integrity, Piston Travel Force, Piston Release Force, expelled volume, Needle Shield Removal Force, consistent with the FDA Guidance - Glass Syringes for Delivering Drug and Biological Products: Technical Information to Supplement International Organization for Standardization (ISO) Standard 11040-4 as well as ISO 11040-4: 2007 Prefilled Syringes—Part 4: Glass Barrels for Injectables have been addressed in this retrospective review of this PFS. However, this testing cannot be located within your submission. The sponsor will need to provide this information.

IV. Design Control Review

A. Design Control Documentation Check

Design Control Requirement*	Signed/Dated Document Present		Submission Location
	Yes	No	
Design Requirements Specifications included in the	X		3.2.P.5.1

NDA / BLA by the Combination Product Developer			
Design Verification Data included in the NDA / BLA or adequately cross-referenced to a master file.	X		3.2.R.2
Risk Analysis supplied in the NDA / BLA by the Combination Product Developer	X		3.2.R.2, section 5
Validation Data	X		3.2.P.5.4, 3.2.P.8.1
Traceability Documentation	X		3.2.R.2

*Sponsor may derive the regulatory requirements from 21 CFR 820.30 into multiple sets of documents. For example, injectors containing software may include separate software requirements and specification documents. In these circumstances, additional rows may need to be added to the table.

Design Requirements/Specifications

Table 1: Release and Stability Specifications for Drug Product

Quality Attribute	Test	Release Acceptance Criteria	Stability Acceptance Criteria
Appearance of Primary Container	Appearance of Primary Container (DS-TMD-4871)		(b) (4)
Color of Solution	Color of Solution (DS-TMD-3736)		
pH	pH (DS-TMD-8795, DS-TMD-3948)		
Osmolality	Osmolality (DS-TMD-8879)		
Turbidity	Turbidity (DS-TMD-18164)		
Particulate Matter (Visible Foreign)	Particulate Matter (Visible foreign) (DS-TMD-13332)		
Particulate Matter (Visible Translucent)	Particulate Matter (Visible Translucent by Micro-flow Digital Imaging) (DS-TMD-13302)		
Particulate Matter (Sub-visible)	Particulate Matter (Sub-visible) (DS-TMD-4874)		
	(b) (4)		
Glidability	Piston Release Force (DS-SOP-5701) Piston Travel Force (DS-SOP-5701)		
Identity	Dot Blot (DS-TMD-3930)		
Charge Heterogeneity	cIEF (DS-TMD-4287)		
Purity	cSDS (reduced) (DS-TMD-4102) cSDS (non-reduced) (DS-TMD-4717) DW-SE-HPLC (DS-TMD-4476)		

Table 1: Release and Stability Specifications for Drug Product

Quality Attribute	Test	Release Acceptance Criteria	Stability Acceptance Criteria
		(Continued)	
Quantity (Protein Concentration)	Absorbance at A ₂₈₀ (DS-TMD-3447)		(b) (4)
Potency	U2OS Bioassay (DS-TMD-20817)		
Pyrogen	Endotoxin (DS-TMD-16844)		
Microbiological Contamination	Sterility (DS-TMD-9203, DS-TMD-16843) Container and Closure Integrity (DS-TMD-17925)		

^a Not applicable; test not performed for stability monitoring.
^b The test is performed at t = 0 as the initial stability reference.

B. Design Verification and Validation Review

Standard / Guidance		Conforms		
		Yes	No	N/A
Syringes	ISO 11040-4 Prefilled Syringes – Glass Barrel for Injectables	X		
	ISO 11040-5: Prefilled syringes - part 5: plunger stoppers for injectables.			X
	ISO 7886, Sterile Hypodermic Syringes for Single Use;			X
Needle	ISO 7864, Sterile Hypodermic Needles for Single Use;	X		
	ISO 9626, Stainless Steel Needle	X		

	Tubing for Manufacture of Medical Devices;			
Sharps Injury Prevention Feature	Guidance for Industry and FDA Staff: Medical Devices with Sharps Injury Prevention Features	X		
	ISO 23908 - Sharps injury protection - Requirements and test methods - Sharps protection features for single-use hypodermic needles, introducers for catheters and needles used for blood sampling	X		
Connections	ISO 594-1: Conical Fittings with 6% (Lure) Taper for Syringes, Needles and Certain Other Medical Equipment - Part 1: General Specifications			X
	ISO 594-2: Conical Fittings with 6% (Lure) Taper for Syringes, Needles and Certain Other Medical Equipment - Part 1: Lock Fittings			X

Design Verification Review

Essential Performance Requirement	Specification	Verification Test Results	
		PASS	FAIL
Break Force	(b) (4)	X	
Glide Force		X	
Expelled Volume		X	
Sharps Injury Protection – Simulated Use Testing		X	

Validation of the glidability procedure was performed in accordance with the ICH Tripartite Guideline Q2 (R1), Validation of Analytical Procedures: Text and Methodology. The glidability analytical procedure is validated for determining the functionality of the prefilled syringe (PFS). The validation of the procedure included instrument accuracy, instrument precision, and method performance. The validation of the

generic procedure was based on assessing repeatability and reproducibility and demonstrated using PFS filled with water for injection (WFI) and glycerol in different concentrations (b) (4). This study design covered both the fill volume and viscosity of PFS with drug product (DP) (100 mg/mL, 1.0 mL PFS). In addition, the validated method was verified for 1 mL PFS active (100 mg/mL) (b) (4).

Table 1: Summary of Acceptance Criteria and Results for the Validation Study

Parameter	Acceptance Criteria	Result	Pass/Fail
Instrument Accuracy	(b) (4)	1.96 N ^a 19.6 N ^a	Pass Pass
Method Performance	(b) (4)	Simulated PFS: ≤15%	Pass
		Simulated PFS: ≤12%	Pass
		18%	Pass
		7	Pass

^a Results reflect the measurements of n = 1 load cell.

PFS = Prefilled syringe
PRF = Piston release force
PTF = Piston travel force
RSD = Relative standard deviation

Table 2: Summary of Acceptance Criteria and Results for the Verification Study

Parameter	Acceptance Criteria	Result	Pass/Fail
Instrument Accuracy	(b) (4)	1.96 ^a 19.6 N ^a	Pass Pass
Instrument Precision	(b) (4)	0.20 kg: 0% RSD	NA
		2.0 kg: 0% RSD	NA
Method Performance	(b) (4)	1.0 mL PFS	
		PRF: ≤9% RSD	Pass
		PTF: ≤20% RSD	Pass
		1.0 mL PFS	
		PRF: ≤8% RSD	Pass
		PTF: ≤16% RSD	Pass

^a Results reflect the measurements of n = 5 load cells.

PFS = Prefilled syringe
PRF = Piston release force
PTF = Piston travel force
RSD = Relative standard deviation
NA = Not applicable, no acceptance criteria established because this is a characterization test only

Table 12: Piston Release Force Results for Drug Product (100 mg/mL, 1.0 mL PFS)

Test Article	Piston Release Force (N)	
	Trial 1	Trial 2
Acceptance Criterion, % RSD, per Trial:	(b) (4)	(b) (4)
Acceptance Criterion, Overall % RSD:	(b) (4)	
1	3.57	3.30
2	3.45	2.90
3	3.49	3.27
4	3.31	3.33
5	2.91	3.63
6	3.08	2.82
7	3.01	3.41
8	3.26	3.28
9	3.72	3.27
10	3.75	3.38
Mean Force (n = 10):	3.36	3.26
Minimum Force:	2.91	2.82
Maximum Force:	3.75	3.63
SD (n = 10):	0.29	0.24
RSD (%) (n = 10) ^a :	9	7
Overall RSD (%) (n = 20) ^a :	8	
Overall Mean (n = 20) ^a :	3.31	

^a Value rounded to the same number of decimal places as acceptance criterion.

PFS = Prefilled syringe
RSD = Relative standard deviation
SD = Standard deviation

Table 13: Piston Travel Force Results for Drug Product (100 mg/mL, 1.0 mL PFS)

Test Article	Piston Travel Force (N)	
	Trial 1	Trial 2
Acceptance Criterion, % RSD, per Trial:	(b) (4)	(b) (4)
Acceptance Criterion, Overall % RSD:	(b) (4)	
1	5.35	6.61
2	5.19	5.34
3	4.09	3.98
4	5.82	4.40
5	5.02	4.02
6	5.32	5.46
7	4.36	4.39
8	4.46	5.79
9	6.13	4.36
10	4.77	6.64
Mean Force (n = 10):	5.05	5.10
Minimum Force:	4.09	3.98
Maximum Force:	6.13	6.64
SD (n = 10):	0.65	1.02
RSD (%) (n = 10) ^a :	13	20
Overall RSD (%) (n = 20) ^a :	16	
Overall Mean (n = 20) ^a :	5.08	

^a Value rounded to the same number of decimal places as acceptance criterion.

PFS = Prefilled syringe
RSD = Relative standard deviation
SD = Standard deviation

Reviewer's Note: The sponsor has conducted glidability testing (break loose/glide force testing) to test the travel force and release force for the syringe. Based on review of the testing, all acceptance criteria were met for all parameters tested in the operating range of the PFS for the Glidability test in both the validation study and the verification study.

Expelled Volume:

The DP is filled with (b) (4) to deliver a nominal 100 mg in 1.0 mL per syringe. An expelled volume test was performed to confirm that the volume expelled from a standard PFS assembled to (b) (4) was not less than the labelled dose. In this test, a bracketed approach was used to verify that the intended dose can be achieved when a PFS is assembled to (b) (4). Pre-filled syringes were filled with representative solution using the validated PFS fill process (b) (4).

The contents of a total of 60 ISO standard PFS (1 mL-long type) with ½" needles assembled to (b) (4) were manually expelled until the needle lock out. Thirty samples were used for each fill volume. Expelled contents were measured gravimetrically and converted to volume based on density of the fluid.

The measured mean expelled volume was (b) (4) mL for 1.0 mL fill PFS. Therefore, it was concluded that the acceptance criteria to deliver the labelled dose was met, as the expelled volume was not less than the labelled dose.

Reviewer's Note: The sponsor has clarified that they have tested expelled volume using (b) (4) ml fill to bracket the dosage to make sure complete dose could be given. This approach is acceptable.

Sharps injury protection feature

(b) (4) needle stick prevention feature is cleared under K (b) (4).

Reviewer's Note: This sharps protection feature has been reviewed in several other applications by this reviewer as well as other reviewers. The simulated use study validating the sharps feature is present within K (b) (4). The manufacturer of the (b) (4) operates under a Design Control System mandated by FDA Quality Systems Regulations and EU MDD (under ISO 13485) to ensure establishment of essential quality aspects including user needs, intended uses, safety, efficacy, performance, and reliability from concept through manufacture. Additional review of the sharps feature is not needed in this case in this reviewer's opinion.

Design Validation Review

Risk Analysis Attributes	Yes	No	N/A
Risk analysis conducted on the combination product	X		

The manufacturer, as well as the Applicant, has performed Failure Modes and Effects Analyses (FMEA) to assess risks and hazards for the (b) (4) assembled with PFS. While not being a stand-alone medical device, the (b) (4) has been evaluated for potential risks associated with design, assembly, performance, and use as a simple (non-sterile, non-measuring) device. The sponsor has reported that Over (b) (4) million units of (b) (4), which are PFS assembled to (b) (4), have been distributed globally since initial marketing (b) (4). Because of the similarity in the design, functionality, and manner of use of the (b) (4) to the proposed (b) (4) for guselkumab (summarized in Section 1.2), it is reasonable to expect that the overall risks to the patient, foreseeable mis-uses, and system hazards would be similar. Historically, the total complaint rate for (b) (4) has been low (i.e. <0.2%) and many of the reported complaints are actually training or use-related issues, not device defects.

Table 2: Hazard/Risk Identification

Hazard Code	Potential Hazards ^a	Example Cause	Harm	Severity ^b
1	Biocompatibility.	Material not qualified or wrong material used during molding. User sensitive to qualified material.	Allergic reaction, dermatitis.	Marginal
2	Wrong dose, over.	Syringe container is not biocompatible. Unable (or choose not) to read, differentiate or understand carton and/or device labels. Counterfeit drug.	No injury to patient. Adverse Event.	Negligible Marginal
3	Wrong dose, under.	Counterfeit drug. Product Stored outside the specified temperature range either during transport or by patient/caregiver. Patient/caregiver fail to note expiration date. Expired product used. Product not stored away from light either during transport or by patient/caregiver. Product is warmed to room temperature using means other than passive heat transfer from room temperature air (i.e. sunlight, microwave oven, etc.). Patient fails to inspect liquid for discoloration, cloudiness, or unacceptably large particles. Patient/caregiver does not understand/follow instructions to let syringe warm outside of refrigerator for required length of time and injection discomfort caused by cold fluid induces early withdrawal of syringe prior to delivering full dose. Syringe barrel breakage or defect and drug leaks out of barrel. Package opening features not functional and device damaged by attempts to remove packaging. Patient/Caregiver does not understand/ follow instructions for removing needle cover and bends needle which breaks after insertion. Needle insertion into skin not perpendicular, too rough causing needle to break. Glide force/Break-loose force too high. Absorptivity - protein concentration in drug product does not meet release specification.	Exacerbation of pre-existing condition.	Marginal
		(Continued)		
4	Needle breaks after insertion.	Needle defect.	Exacerbation of pre-existing condition. Pain, patient discomfort.	Marginal Negligible
5	Product degradation leading to aggregate formation.	Product stored outside the specified temperature range either during transport or by patient/caregiver. Patient/caregiver fails to note expiration date. Expired product used. Product not stored away from light either during transport or by patient/caregiver. Product is warmed to room temperature using means other than passive heat transfer from room temperature air (i.e. sunlight, microwave oven, etc.). Patient fails to inspect liquid for discoloration, cloudiness, or unacceptably large particles.	Adverse Experience. Serious Adverse Experience. Exacerbation of pre-existing condition.	Marginal Critical Marginal
6	NA	NA	NA	NA
7	Biocontamination.	Patient or caregiver fails to wash hands or cleanse injection site with available accessories. Injection accessories e.g. alcohol swab/cotton ball missing from kit and patient does not cleanse injection site. User blows on skin subsequent to preparing injection site. Prefilled syringe is dropped or touched after removing the needle shield. Plunger removed from syringe.	Local Infection.	Marginal
8	Excessive needle force on skin.	Needle insertion and pull out force not acceptable for intended use.	Pain, patient discomfort.	Negligible
9	Needle could remain after injection.	Needle pull off force from syringe too low.	Transient injury to patient.	Minimal
10	(b) (4)	(b) (4)	Patient has injection site reaction.	Minimal

Hazard Code	Potential Hazards ^a	Example Cause (Continued)	Harm	Severity ^b
11		(b) (4)	No measurable effect.	Negligible
12	Compromised container closure integrity.	Syringe container cracked.	Patient receives contaminated product.	Critical
13	Patient receives contaminated product.	Shelf Life of Syringe (not filled) Exceeded.	Serious Adverse Experience.	Critical
14	Excessive extractables/leachables in PFS.	Formal extractables/leachables study shows not in acceptable range with drug.	Patient has injection site reaction.	Minimal
15	Product may contain discoloration, flecks	Chemical resistance/stability of syringe components are not stable.	Patient has injection site reaction.	Minimal
16	Product may contain protein aggregation.	Max (b) (4) concentration exceeded.	Lack of effect.	Minimal
17	Accidental mechanical damage.	Device damaged by crushing. Device damaged by: Dropping Tampering Patient/caregiver when trying to open box Expired product Failure to read/understand instructions	Adverse experience. Delayed administration of drug.	Critical Negligible
18	Needlestick, patient.	Product defect (b) (4) causing needle guard activation failure. Patient/caregiver does not understand/follow instructions for disposal, sharps container or equivalent not available-leading to improper disposal.	Pain. Cut.	Marginal Marginal
19	Needlestick, caregiver or other individual.	Product defect (b) (4) causing needle guard activation failure. Patient/caregiver does not understand/follow instructions for disposal, sharps container or equivalent not available-leading to improper disposal.	Infection due to blood-borne pathogen.	Catastrophic

Hazard Code	Potential Hazards ^a	Example Cause (Continued)	Harm	Severity ^b
20	Needlestick from unused product.	Needle shield missing while device is still in package, Patient/caregiver contacts needle when removing from package. Needle shield pull-off force too high.	Pain. Cut.	Marginal Marginal
21	Choking due to partial airway obstruction.	Aspiration of needle shield due to any of the following: Patient/caregiver does not understand or follow directions for removal of rubber needle shield and uses teeth to remove. Product being warmed outside of package is tampered with by child or other person.	Hypoxia.	Critical
22	Patient cannot properly inspect the liquid in syringe and determine it is cloudy, discolored, or contains large particles resulting in administration of degraded product.	Visibility limited by syringe label.	Adverse experience. Injection site irritation; allergic reaction.	Marginal Marginal
23	Reasonably foreseeable misuse.	Incorrect injection site. Supplies not available (ie, alcohol swab) resulting in small amount of bleeding at injection site.	Exacerbation of pre-existing condition. Adverse experience. Injection site irritation; allergic reaction.	Marginal Marginal Marginal
24	Drug delivered to wrong person.	Unable (or choose not) to read, differentiate or understand carton and/or device labels. Someone other than the user tampers with device.	Infection due to blood-borne pathogen. Disease unabated. Adverse Experience.	Catastrophic Marginal Critical
			Serious Adverse Experience.	Catastrophic

^a This table includes functional hazards associated with the (b) (4) combination product as well as additional hazards related to the PFS.

^b Severity ratings risk categories descriptions are provided in Table 3.

NA = Hazard ID is not applicable to (b) (4)

		Severity Classification	
Classification	Category	Description	Description
Catastrophic	Patient Impact	Serious adverse experience. Potential for death (e.g. a failure in the product or procedure can lead to patient death.)	
	Product	Complete failure of the product to perform as intended or a performance degradation of multiple Critical Quality Attributes.	
	Regulatory/Compliance	Submission - Revoke license Notification - BPDR (Biological Product Deviation Report) resulting in a class 1 or 2 recall Enforcement - Seizures; injunctions; prosecutions Potential legal action	
	Process	Catastrophic equipment or process failure resulting in employee hazard or harm. Process is shut down. Batch rejected	
Critical	Patient Impact	Serious injury. May cause permanent impairment to the patient or user (e.g. loss of limb or bodily function, allergic reaction or other condition requiring medical intervention).	
	Product	Performance degradation of a single critical quality attribute or multiple Critical Quality Attributes without the potential to exceed acceptable limits.	
	Regulatory/Compliance	Submission - Refusal to file or non-approvable letter received. Inspection - FDA status - official action indicated from Health authority resulting in a regulatory action such as Consent decree/Warning letter/Health Authority sanctions Fail Pre-Approval Inspection Major Field Action	
	Process	Equipment failure effecting a critical process parameter. May be outside of license claims. Requires revalidation or change request. Results in delayed batch release or major impact to manufacturing schedule. Batch may be rejected.	
Marginal	Patient Impact	Non-serious injury. May cause significant but recoverable injury to the patient or user (e.g. febrile response, pain/cut or other condition requiring medical intervention).	
	Product	Performance degradation of multiple non Critical Quality Attributes or a potential impact to a Critical Quality Attribute without the potential to exceed acceptable limits.	
	Regulatory/Compliance	Submission - Agency requests filing categorization upgrade, impacts schedule and causes delays. Inspection - Health Authority status - inspection outcome dependent on substantial corrective active committed in response voluntary action indicated. Health Authority inspection report with deficiencies indicated	
	Process	Failure impacts a critical process parameter resulting in an event. May delay batch release or have a major impact to manufacturing schedule.	

Severity Classification		
Classification	Category	Description
(Continued)		
Minimal	Patient Impact	May cause transient, self-limiting illness or injury to patient or user, (e.g. fever, nausea, bruise or other condition typically not requiring medical intervention).
	Product	Performance degradation of a single Critical Quality Attribute
	Regulatory/Compliance	Submission - Agency contacts us and requests information; response is provided in writing with no impact the schedule or submission. Inspection- HA status – No action indicated
Negligible	Process	Results in an event. Minimum impact to the manufacturing schedule. Event easily recognizable.
	Patient Impact	No illness or injury to patient or user. Inconvenience to user (e.g. procedure was successful, but performance was slow and/or cumbersome).
	Product	No pragmatic impact to Quality Attributes.
	Regulatory/Compliance	Submission- Agency contacts us with minor comments. No impact to schedule or submission. No GMP observation
	Process	Does not affect equipment performance

C. Labeling

Syringe Barrel Label	(b) (4)
Primary Package Label	(b) (4)

Reviewer's Note: The provided labeling looks appropriate for the syringe. Further review will be conducted by CDER/DMEPA.

D. Design Transfer Activities – Release Specifications

After assembly, functional performance testing of the PFS is verified as part of release testing. PFS (b) (4)

Release testing of the PFS (b) (4) consists of visual defects and functionality testing and is described in 3.2.P.5.2 Analytical Procedures, Visual Defects and Functionality Test.

Attribute	Release and Stability Specifications	Test Method
Glidability	(b) (4)	Analytical bench testing
Expelled Volume	(b) (4)	Analytical bench testing

Table 1: Release and Stability Acceptance Criteria for the Visual Defects/Functionality Test for Prefilled Syringe Assembled with (b) (4) 100 mg/syringe)

Test	Release Acceptance Criteria	Stability Acceptance Criteria
Visual Defects/Functionality	Needle guard extended and locked	Not applicable
Expelled Volume	Expelled Volume (DS-TMD-4875)	(b) (4)
Glidability	Piston Release Force (DS-SOP-5701) Piston Travel Force (DS-SOP-5701)	(b) (4)

Biocompatibility: Biocompatibility testing has been conducted by (b) (4), the manufacturer of (b) (4) which is the device constituent of the combination product under K (b) (4), DMF (b) (4) and DMF (b) (4). The Sponsor has not specified any change to the materials of manufacture of the (b) (4) for use in the final guselkumab combination product. After sending an IR, the (b) (4) has provided the biocompatibility testing that was conducted. Summary has been provided in the review, however full testing was provided in the IR response.

1 Page(s) has been Withheld in Full as B4 (CCI/TS) immediately following this page

(b) (4)

Shipping Studies: The sponsor conducted a shipping qualification study (DS-TEC-90526) to demonstrate that shipping of the prefilled syringe assembled with the (b) (4) in the to-be-marketed carton package does not adversely affect PFS (b) (4) performance or container closure integrity. All samples were cartoned and packaged at the maximum capacity shipping configuration that accounts for parameters such as maximum stacking height and maximum shipping weight. PFS (b) (4) test samples were identical to commercial product except for plunger rod color, and assembled and packaged on commercial production lines. Samples were subjected to testing in accordance with ASTM D4169 Standard Practice for Performance Testing of Shipping Containers and Systems.

Testing was conducted with the (b) (4) assembled with PFS containing placebo in (b) (4) 1.0 mL volumes. Use of these volumes represents a bracketing approach that is able to verify the guselkumab commercial presentation ((b) (4) 100 mg in 1.0 mL). The container closure system for both placebos is the same as for the commercial drug product. For visual defects and functionality testing, 150 units of each configuration (1.0 mL Placebo (b) (4)) were tested. Following simulated shipping, container closure integrity by dye ingress testing was conducted on 150 units of each configuration.

Table 2: Simulated Transportation Study Level II Test Sequence with PFS

Hazard Element	Purpose
Schedule A – Manual Handling: Initial Manual Handling Test	Intended to determine the ability of the shipping unit to withstand the hazards, occurring during manual handlings, such as loading, unloading, stacking, sorting, or palletizing. The main hazards from these operations are the impacts caused by dropping or throwing.
Schedule F – Loose Load Vibration	Intended to determine the ability of the shipping unit to withstand the repetitive shocks occurring during transportation of bulk or loose loads (i.e., parcel distribution). The test levels and test method account for amplitude, direction, and duration of repetitive shocks.
Schedule E – Vehicle Vibration	Intended to determine the ability of the shipping units to withstand the vertical vibration environment during transport, and the dynamic compression forces resulting from vehicle stacking. The test levels and methods account for the magnitude, frequency range, duration, and direction of vibration.
Schedule A – Manual Handling: Second Manual Handling Test	Intended to determine the ability of the shipping unit to withstand the hazards, occurring during manual handlings, such as loading, unloading, stacking, sorting, or palletizing. The main hazards from these operations are the impacts caused by dropping or throwing.
Schedule I – Low Pressure	Intended to provide for the anticipated reduction in pressure when packaged products are transported via certain modes, such as cargo aircraft or by ground over mountain passes.

Table 3: Test Results of the Simulated Transportation Study for PFS

Test	Acceptance Criteria ^a	Results			
		Control PFS		PFS After Simulated Transportation	
		(b) (4)	100 mg	(b) (4)	100 mg
Color of Solution	(b) (4)	≤B6	≤B6	≤B6	≤B6
		≤BY6	≤BY6	≤BY6	≤BY6
		≤Y6	≤Y6	≤Y6	≤Y6
Expelled Volume		0.5	1.0	0.6	1.0
Glidability		4.4	4.2	4.0	4.0
		6.0	7.2	4.8	5.9

Table 5: Shipping Tests Results

Test	Acceptance Criteria	Result
Visual Defects/Functionality	(b) (4)	Pass
Container Closure Integrity (CCI)		Pass

Table 4: Plunger Stopper Movement at Simulated Altitudes

Test (acceptance criteria)	Simulated Altitude			
	8,000 ft (after 3 exposures)	12,000 ft	16,000 ft	20,000 ft
Range of plunger stopper movement for (b) (4) 1.0 mL fill volumes (b) (4) mm ^a	2.22-3.92 mm	2.51-3.29 mm	3.71-4.72 mm	4.48-6.80 mm

^a Sterility would not be impacted if the observed stopper movement or the sum of observed plunger stopper movement was less than the plunger stopper sterile barrier height of (b) (4) mm, which was defined as the distance between the plunger stopper shoulder and 3rd rib.

V. Information Requests

Sent March 8, 2017

Janssen Research has referred that biocompatibility testing could be found in DMF (b) (4) and DMF (b) (4). However, we are unable to locate it within DMF (b) (4) or (b) (4). Please provide summary biocompatibility testing for the PFS and needle shield.

Reviewer's Reponse: (b) (4) has provided the biocompatibility testing.

Sent February 15, 2017

You have stated that elements of Design Controls per 21 CFR 820.30 have been taking into account in relation to user needs, intended uses, safety, efficacy, performance, and reliability. The applicable functional requirements, for example: Seal Integrity, Piston Travel Force, Piston Release Force, expelled volume, Needle Shield Removal Force, consistent with the FDA Guidance - Glass Syringes for Delivering Drug and Biological Products: Technical Information to Supplement International Organization for Standardization (ISO) Standard 11040-4 as well as ISO 11040-4: 2007 Prefilled Syringes—Part 4: Glass Barrels for Injectables have been addressed in this retrospective review of this PFS. However, this testing cannot be located within your submission. Please provide this information.

Reviewer's Response: The sponsor has provided reference to the testing in the following locations:

Seal Integrity: 3.2.P.2.5

Table 1: CCI Testing Acceptance Criteria and Results After Assembly of the Plunger Rod to the Plunger of Three Batches of PFS

Control Type	Acceptance Criteria	Batch ID EIS7P	Batch ID DIS6S	Batch ID EES6J
Tested Syringes	(b) (4)	Complies	Complies	Complies

The validation tests performed demonstrate that PFS maintain CCI subsequent to the plunger rod assembly process.

Piston Travel/Release Force: 3.2.P.8.3, pages 4-186

Expelled Volume: 3.2.R.2, section 7.11

Mean expelled volume was (b) (4) and (b) (4) mL for 1.0 mL fill PFS.

Needle Shield Removal Force:

Table 1: Needle Shield Removal Force Results Summary

Continuous measurement	Acceptance criteria	Measured avg./min./max.	Standard deviation	Normal distribution	K factor	Pass
Needle shield removal force	(b) (4)	13.0/10.4/17.9	1.85	yes	17.3 (>2.2)	YES

You have stated that you have added the Letter of Authorization to reference K (b) (4) to Module 1.4.1 Letter of Authorization. However, this LOA still cannot be located. Please specify the exact location and date where this LOA can be found.

Reviewer's Note: The LOA was added to 1.4.1 within the submission in Sequence 009 under the CMC Response to FDA communication.

You have provided the biocompatibility of the needle safety feature but not the syringe. Please provide the location of the biocompatibility of the syringe.

Reviewer's Note: The sponsor states that biocompatibility is present in DMF (b) (4) (for the syringe) and DMF (b) (4) (for the needle shield) since the biocompatibility is not altered by the manufacturing process. Studies to determine the extractables and leachables from the syringe plunger stopper and rigid needle shield were conducted, and met the requirements of ISO 8871 and USP <381>. These studies have been described in 3.2.P.2.4,

Please provide the location of the testing for the syringe and needle based on ISO 11040-4 Prefilled Syringes – Glass Barrel for Injectables, ISO 11040-5: Prefilled syringes - part 5: plunger stoppers for

injectables., ISO 7864, Sterile Hypodermic Needles for Single Use; and ISO 9626, Stainless Steel Needle Tubing for Manufacture of Medical Devices

Reviewer's Response: The sponsor has outlined the relevant sections of 11040-4 and 11040-5, whether information on testing to each section of the standard is available, the party that is responsible for the information, and the document reference if available. They have stated that to comply with ISO 7864, the needle bond strength is tested according to ISO 7864, section 13.1 – "Bond between hub and needle tube." In relation to needle, testing would be provided by (b) (4) within the DMF.

Relevant Section	Relevant Available Information	Responsible	Comments/Document Reference
5.1 Syringe barrel design including dimensions	Conformity demonstrated to previous version of ISO11040-4, Section 3.1, Dimensions, except for Section 3.2, Designation	(b) (4)	Attachment 1: DS-REF-78676, (b) (4) Quality Statement – ISO 11040-4, dated April 23, 2014
5.2 Functional Testing of Luer connection	N/A	N/A	N/A
5.3 Material	Conformity demonstrated to previous version of ISO11040-4, Section 4.2.1: Glass Type I of the EP3.2.1 or USP <660>; and Section 4.2.2	(b) (4)	Attachment 1: DS-REF-78676, (b) (4) Quality Statement – ISO 11040-4, dated April 23, 2014
5.4 Performance requirements			
5.4.1 Hydrolytic Resistance	Conformity demonstrated to previous version of ISO11040-4, Section 4.3.1, Hydrolytic Resistance	(b) (4)	Attachment 1: DS-REF-78676, (b) (4) Quality Statement – ISO 11040-4, dated April 23, 2014
5.4.2 Annealing Quality	Conformity demonstrated to previous version of ISO11040-4, Section 4.3.2, Annealing quality	(b) (4)	Attachment 1: DS-REF-78676, (b) (4) Quality Statement – ISO 11040-4, dated April 23, 2014
	(b) (4)	Janssen	3.2.P.2.4 Container Closure System
5.4.4 Flange breakage resistance	Flange resistance	(b) (4)	Attachment 2: (b) (4) Medical Conformity Certificate for Catalog number (b) (4)
(b) (4)			
6.1 General			
6.1.1 Design varies due to intended use	N/A	N/A	N/A
6.1.2 Properties to be considered: a) Microbial barrier b) Biocompatibility and tox c) Physical and chemical properties d) ability for sterilization e) maintenance of sterility f) Shelf-life g) functionality for intended use h) robustness of closure	Janssen has considered these properties in the selection of this PFS for the guselkumab combination product	Janssen	Internal design control documentation as outlined in 3.2.P.7 Container Closure System

Table 2: ISO 11040-4 Summary			
Relevant Section	Relevant Available Information	Responsible	Comments/Document Reference
(Continued)			
6.1.3 Manufacturer shall have documented procedures for design and development	Janssen has documented procedures for design and development of combination product: filled PFS assembled with (b) (4)	Janssen	3.2.P.7 Container Closure System 3.2.R.2 Medical Device – (b) (4)
6.2 Sterility	(b) (4)	(b) (4)	Attachment 2: (b) (4) Medical Conformity Certificate for Catalog number (b) (4)
6.3 Pyrogenicity/endotoxins	a) Janssen performs pyrogenicity and endotoxin testing for batch release of PFS filled with DP b) PFS: Endotoxins per EU Pharmacopoeia (2.6.14 Bacterial endotoxins) and USP <85> Bacterial endotoxins test less than 1 EU/barrel	a) Janssen b) (b) (4)	a) 3.2.P.5.4 Batch Analysis b) Attachment 2: (b) (4) Medical Conformity Certificate for Catalog number (b) (4)
6.4 Particles	a) Janssen performs batch analysis inspection for visible particulate matter, visible translucent particles, sub-visible particulate matter after filling for release b) Particle counts	a) Janssen b) (b) (4)	a) 3.2.P.5.4 Batch Analysis b) Attachment 2: (b) (4) Medical Conformity Certificate for Catalog number (b) (4)
6.5 Additional requirements to specific components			
6.5.1 Barrel			
6.5.1.1 Refer to section 5 (b) (4)	N/A (b) (4) content on barrel measured for development, clinical, and process validation batches	N/A Janssen	N/A 3.2.P.2.4 Container Closure System
6.5.1.3 Dead space in barrel and nozzle when plunger fully inserted determined as in ISO 7886-1:1993 Annex C	Janssen conducted expelled volume testing, demonstrating that fill volume enables full dose to be delivered, taking into account dead space with plunger fully inserted	Janssen	Batch release: expelled volume testing: 3.2.P.5.4, Batch Analysis Stability: 3.2.P.8.1, Stability Summary and Conclusion; 3.2.P.8.3, Stability Data, PFS
6.5.2 Needle			
6.5.2.1 Reference 6.5.2.2 to 6.5.2.4			
6.5.2.2 Material, dimension, design requirements			
6.5.2.2 ISO 9626: Needle material and dimensions	Needle material specified as AISI 304 Stainless steel	(b) (4)	Attachment 2: (b) (4) Medical Conformity Certificate for Catalog number (b) (4)

Table 2: ISO 11040-4 Summary			
Relevant Section	Relevant Available Information	Responsible	Comments/Document Reference
(Continued)			
6.5.2.2 ISO 7864: Needle bevel, dimensions, and bond between needle and glass	a) Needle pull out force (b) (4) b) Needle point quality	a) (b) (4) b) (b) (4)	a) See statement in response to Question 2 above b) Attachment 2: (b) (4) Medical Conformity Certificate for Catalog number (b) (4)
6.5.2.2 ISO 7864: Actual needle length	Unknown	(b) (4)	
6.5.2.3 Needle shall be lubricated	(b) (4)	(b) (4)	Attachment 2: (b) (4) Medical Conformity Certificate for Catalog number (b) (4)
6.5.2.4 Needle patency (ISO 7864)	Unknown	(b) (4)	
	(b) (4)	(b) (4)	Attachment 2: (b) (4) Medical Conformity Certificate for Catalog number (b) (4) Attachment 3: (b) (4) ISO10993 Compliance Statement Also referenced in 3.2.P.2.4, Container Closure System
6.5.3 Closure System			
6.5.3.1 Material that can contact product meets ISO 8871-1	Plunger stopper and rigid needle shield meet density, ash, IR Spectra according to ISO 8871-2	(b) (4)	Attachment 2: (b) (4) Medical Conformity Certificate for Catalog number (b) (4) Also referenced in 3.2.P.7 Container Closure System
6.5.3.2 Closure system shall allow for sterilization	(b) (4)	(b) (4)	Attachment 2: (b) (4) Medical Conformity Certificate for Catalog number (b) (4)
6.5.3.3 Closure system allow for proper liquid leakage resistance (from needle shield)	Leak test	(b) (4)	Attachment 2: (b) (4) Medical Conformity Certificate for Catalog number (b) (4)
6.5.3.4 N/A	N/A	N/A	N/A
6.5.3.5 N/A	N/A	N/A	N/A
6.5.3.6 N/A	N/A	N/A	N/A
6.5.3.7 Needle shield can be removed with reasonable pull off force	Needle shield removal force (b) (4)	a) (b) (4) b) Janssen	a) (b) (4) Design Verification Report (b) (4) reviewed by Janssen during audit of (b) (4) b) See response to Question 1
6.5.3.7 Needle shield maintains sterility of needle	Unknown	(b) (4)	
Table 2: ISO 11040-4 Summary			
Relevant Section	Relevant Available Information	Responsible	Comments/Document Reference
(Continued)			
6.6 Closure system barrel integrity	Janssen performs Container Closure Integrity Testing (CCIT) on PFS filled with drug product	Janssen	Process validation: 3.2.P.2.5, Microbiological Attributes: 3.2.P.5.4, Batch Analysis: 3.2.P.8.1, Stability Summary and Conclusion; 3.2.P.8.3, Stability Data, PFS Shipping: 3.2.P.3.5, Process Validation and/or Evaluation, Shipping Qualification
7 N/A	N/A	N/A	N/A
8 N/A	N/A	N/A	N/A

Table 3: ISO 11040-5 Prefilled Syringes – Plunger Stoppers for Injectables			
Relevant Section	Relevant Available Information	Responsible	Comments/Document Reference
4 Shape and dimensions			
4.1 Shape and dimensions as in standard	Dimensions	(b) (4)	(b) (4) Attachment 4: (b) (4) Medical Conformity Certificate for Catalog number (b) (4) Dimensions summarized in 3.2.P.7, Container Closure System
4.2 Dimensional tolerances	Dimensions	(b) (4)	(b) (4) Attachment 4: (b) (4) Medical Conformity Certificate for Catalog number (b) (4) Dimensions summarized in 3.2.P.7, Container Closure System
4.3 Spacers	Unknown	(b) (4)	
4.4 Sprues	Unknown		
4.5 Performance of stopper thread shall be compatible with plunger rod	Functional with Hypak syringes		(b) (4) Attachment 4: (b) (4) Medical Conformity Certificate for Catalog number (b) (4)
5 Designation	Unknown	(b) (4)	
6 Material			
6 Tested and approved by end user	Density, ash, IR spectra according to ISO 8871-2	(b) (4)	(b) (4) Attachment 4: (b) (4) Medical Conformity Certificate for Catalog number (b) (4) Also referenced in 3.2.P.7 Container Closure System
6 Withstand two sterilization cycles	Unknown	(b) (4)	
7 Requirements			
7.1 General			
7.2 Physical Requirements			
7.2.1 Hardness (ISO 7619-1 or ISO 48)	Unknown	(b) (4)	
7.2.2 Resistance to aging	Stability studies performed on PFS filled with drug product	Janssen	3.2.P.8.1, Stability Summary and Conclusion; 3.2.P.8.3, Stability Data, PFS
7.3 Chemical requirements (ISO 8871-1)	Density, ash, IR spectra according to ISO 8871-2	(b) (4)	(b) (4) Attachment 4: (b) (4) Medical Conformity Certificate for Catalog number (b) (4) Also referenced in 3.2.P.7 Container Closure System
7.4 Biological Requirements (ISO 8871-4)	ISO 10993-1	(b) (4)	(b) (4) Attachment 4: (b) (4) Medical Conformity Certificate for Catalog number (b) (4) (b) (4) Attachment 3: (b) (4) ISO10993 Compliance Statement Also referenced in 3.2.P.7 Container Closure System
8 Labeling	N/A	N/A	N/A

Sent January 9, 2017: IR comments were responded to and resolved

We are unable to locate the following information:

- LOA for the K (b) (4) and K (b) (4)
- Essential performance specifications
- Design verification and validation testing of the combination product (I see it for the needlestick feature but not overall such as dose accuracy, breakloose/glide force, etc.)
- Design and lot release specifications for the device (nothing on device in 3.2.P.5.1)
- Risk analysis for final device constituent of combination product
- Biocompatibility testing
- Shipping studies

VI. Outstanding Deficiencies: None

VII. Post-Market Commitments / Post-Market Requirements: None

VIII. Recommendation: Approval

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

/s/

MATTHEW E WHITE

03/22/2017

Device review entered into DARRTS on behalf of CDRH



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: February 10, 2017

From: CDER DCRP QT Interdisciplinary Review Team

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

To: Matthew White
DDDP

Subject: QT-IRT Consult to BLA 761061

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 11/21/2016 regarding the division's question about the QT prolongation potential for guselkumab. The QT-IRT received and reviewed the following materials:

- Your consult;
- Highlights of Clinical Pharmacology and Cardiac Safety;
- Module 2- Introduction;
- Module 2- Summary of Clinical Safety for CNTO1959 (guselkumab);
- Study reports for PSO3001 and PSO3002; and
- Analysis datasets (ADEG) from PSO3001 and PSO3002.

QT-IRT Comments for DDDP

Question from the Division: Janssen Biotech, Inc., has submitted BLA 761061 for guselkumab, a human IgG1 λ monoclonal antibody that binds to human IL-23. The proposed indication is treatment of moderate to severe plaque psoriasis in patients who are candidates for systemic therapy or phototherapy. Guselkumab was evaluated under IND 105004. ECGs performed during the development program have been submitted to the ECG warehouse. Please review and

comment regarding the potential of guselkumab to cause prolongation of the QT interval, or to otherwise negatively affect cardiac rhythm.

QT-IRT's response: Large targeted proteins and monoclonal antibodies, such as guselkumab, have a low likelihood of direct ion channel interactions and low risk for QT prolongation. We have reviewed the provided non-clinical and clinical information, which supports that guselkumab does not prolong the QT interval.

BACKGROUND

Guselkumab (CNTO 1959) is a fully human immunoglobulin G1 lambda (IgG1 λ) mAb that binds to the p19 protein subunit of human interleukin 23 (IL-23) with high specificity and affinity. Guselkumab has a molecular weight of 146,613 Daltons and an isoelectric point range of 8.8 to 9.1. It contains 1 N-linked oligosaccharide on each heavy chain of the molecule. It has not yet been assigned an Anatomical Therapeutic Chemical (ATC) code.

Guselkumab (CNTO 1959) is directed against the p19 subunit of IL-23 and thus, specifically targets IL-23. A rapidly growing body of literature suggests that the IL-23/IL-17 pathway contributes to the chronic inflammation underlying the pathophysiology of many immunemediated diseases, including psoriasis. Susceptibility to psoriasis has been shown to be associated with genetic polymorphisms in IL-23/IL-23 receptor (IL-23R) components.

This Biologics License Application (BLA) presents data to support the use of guselkumab for the treatment of adults with moderate-to-severe plaque psoriasis who are candidates for systemic therapy or phototherapy.

Preclinical Cardiac Safety:

In vitro, the hERG assay which is standardly conducted for small molecule drugs, was not considered appropriate for guselkumab since large molecule drugs such as guselkumab have low/no potential to interact with the intra- and extracellular domains of the hERG channel (Vargus et al, 2008)³. Guselkumab was, however, evaluated in-vitro in non-GLP and GLP tissue cross-reactivity studies using human and cynomolgus monkey (cross-reactive toxicology species) tissues to assess the potential of guselkumab to bind to unintended targets. Results revealed cytoplasmic staining to both skeletal and cardiac myocytes; however, the in vitro cytoplasmic staining of myocytes was not considered to be relevant to in vivo administration because antibodies are too large to diffuse across plasma membranes and are unable to gain access to the intracellular environment.

In vivo, potential CV risk associated with guselkumab administration was evaluated in the 5-week subchronic/24-week chronic repeated dose toxicology study, and separately in a CV safety pharmacology study, both in the cynomolgus monkey. There were no treatment-related adverse effects on safety pharmacology parameters in cynomolgus monkeys administered ≤ 50 mg/kg/week guselkumab IV for 5 weeks or SC for up to 24 weeks. Results from the CV study indicated no adverse effects of guselkumab on any of the CV parameters evaluated (systolic, diastolic and mean arterial pressure; electrocardiograms [PR, QRS, RR, QT, and QTcB (Bazett's)]; heart rate; body temperature). There was no cytoplasmic staining of myocytes detected by IHC when guselkumab was administered systemically to monkeys.

Published peer reviewed literature indicates a potential role for inhibition of IL-23 (and IL-17) in slowing or reversing coronary artery disease (CAD) progression (eg, Abbas et al, 2015),¹ although there is some conflicting literature that indicates a beneficial role for presence of IL-23 in CAD (eg, Savvatis et al, 2014).²

Taken together, the weight of the preclinical evidence does not support an increased risk of CV events in the setting of IL-23 blockade with guselkumab (Mod2.4/NCO and Mod2.6.7/Tox Tabulated Summary).

Clinical Cardiac Safety:

- A summary of the 6 core psoriasis studies, including the number of subjects in each study exposed to guselkumab and the corresponding dose levels, is provided in Table 2 (also presented in the Summary of Clinical Safety, Mod2.7.4/Sec 1.1.1.1). Adverse Events (AEs) after Week 16 treatment for randomized subjects in CNTO1959PSO3003 and after exposure to study agent at Week 0 (control or guselkumab) for the other 5 studies were searched for all of the AE preferred terms included in the Standard MedDRA Query (SMQ) terms for Torsades de pointes/QT prolongation (provided in attached Table 3). These searches yielded a total of 2 AEs of syncope, which are summarized in Table 4. These events, both from the CNTO1959PSO3002 study, occurred in subjects who were randomized to placebo after they crossed over to guselkumab. One of these events was serious, and occurred in a 44 year-old woman with a history of psoriasis, psoriatic arthritis, and migraines who had a headache and fainted. She was hospitalized, and her evaluation included a head CT, brain MRI and EEG, which were all unremarkable. She was treated with sumatriptan, Axotal, and valproate semisodium, and was discharged 3 days later with diagnoses of headache and syncope. The second event was a nonserious event that occurred in a 35 year-old woman with no reported medical history other than psoriasis. The event was reported as “swoon”, characterized as mild by the investigator and occurred on the same date as an AE of diarrhea. No medical records were available for this event.
- A thorough QT study was not performed for guselkumab; however, the safety assessment for guselkumab included collection of sufficient ECG data to exclude a clinically important effect on cardiac electrical activity, including the QT interval. There was no evidence for any clinically meaningful changes from baseline in ECG interval values in the pooled safety analysis set (CNTO1959PSO3001 and CNTO1959PSO3002), nor in the other core psoriasis studies or the completed studies in other indications or populations (Mod2.7.4/Sec4.2). In addition, across the clinical development program, there was no evidence for treatment-related changes in BP or pulse rate in subjects exposed to guselkumab (Mod2.7.4/Sec4.1).

QT assessment:

A thorough QT study was not performed for guselkumab. The ICH E14 guideline regarding the clinical evaluation of QT/QTc interval prolongation and proarrhythmic potential for nonantiarrhythmic drugs does not specifically address QT assessments for biologic agents. Recent publications, however, indicate a consensus that, because of their large size and high target specificity, mAbs such as guselkumab have a very low likelihood for ion channel interactions and therefore thorough QT/QTc studies are not generally needed.^{37,44} Importantly,

the safety assessment for guselkumab included collection of sufficient ECG data to exclude a clinically important effect on cardiac electrical activity, including the QT interval.

Key findings concerning analysis of ECG data in the Phase 3 studies PSO3001 and PSO3002 are as follows:

- For the pooled safety analysis set, the frequency of new postbaseline ECG abnormalities was low and occurred at comparable rates for the guselkumab and adalimumab groups, and the types of recorded abnormalities appeared similar for the two groups.
- There was no evidence for any clinically meaningful changes from baseline in ECG interval values in the pooled safety analysis set (nor in the other core psoriasis studies or the completed studies in other indications or populations).

Reviewer's Comment: Large targeted proteins or monoclonal antibodies, such as guselkumab, have a low likelihood of direct ion channel interaction, and unless proarrhythmic risk is suggested by mechanistic considerations or data from nonclinical or clinical studies a thorough QT study is not required to assess the potential for QT prolongation (ICH E14 Q&A (R3), 6.3). The nonclinical and clinical data reviewed do not suggest a potential for QTc prolongation. To further support the clinical assessment, an outlier analysis was conducted, see the tables below, which does not support a potential for QTc prolongation for guselkumab.

Outlier analysis for PSO3001:

Table 1: Outlier analysis for study PSO3001 through week 48

Treatment Group	Total N		450 < QTcF ≤ 480 ms		480 < QTcF < 500 ms		QTcF > 500 ms	
	Subj. #	Obs. #	Subj. #	Obs. #	Subj. #	Obs. #	Subj. #	Obs. #
Adalimumab	326	630	11 (3.3%)	13 (2.1%)	1 (0.3%)	2 (0.3%)	0 (0%)	0 (0%)
Guselkumab	326	636	16 (4.7%)	18 (2.8%)	1 (0.3%)	1 (0.2%)	0 (0%)	0 (0%)
Placebo	167	329	5 (2.9%)	7 (2.1%)	1 (0.6%)	1 (0.3%)	0 (0%)	0 (0%)

Table 2: Outlier analysis for change from baseline for study PSO3001 through week 48

Treatment Group	Total N		30 < ΔQTcF ≤ 60 ms		ΔQTcF > 60 ms	
	Subj. #	Obs. #	Subj. #	Obs. #	Subj. #	Obs. #
Adalimumab	324	626	18 (4.1%)	18 (2.9%)	1 (0.2%)	1 (0.2%)
Guselkumab	324	632	12 (2.7%)	13 (2.1%)	0 (0%)	0 (0%)
Placebo	167	329	8 (3.6%)	9 (2.7%)	1 (0.4%)	1 (0.3%)

Outlier analysis for PSO3002 (week 16):

Table 3: Outlier analysis for study PSO3002 (week 16)

Treatment Group	Total N		450 < QTcF <= 480 ms		480 < QTcF < 500 ms		QTcF > 500 ms	
	Subj. #	Obs. #	Subj. #	Obs. #	Subj. #	Obs. #	Subj. #	Obs. #
Adalimumab	234	234	2 (0.9%)	2 (0.9%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Guselkumab	473	473	11 (2.3%)	11 (2.3%)	1 (0.2%)	1 (0.2%)	0 (0.0%)	0 (0.0%)
Placebo	229	229	4 (1.7%)	4 (1.7%)	0 (0%)	0 (0%)	1 (0.4%)	1 (0.4%)

Table 4: Outlier analysis for change from baseline for study PSO3002 (week 16)

Treatment Group	Total N		30 < ΔQTcF <= 60 ms		ΔQTcF > 60 ms	
	Subj. #	Obs. #	Subj. #	Obs. #	Subj. #	Obs. #
Adalimumab	234	234	1 (0.4%)	1 (0.4%)	0 (0%)	0 (0%)
Guselkumab	473	473	11 (2.3%)	11 (2.3%)	0 (0%)	0 (0%)
Placebo	227	227	6 (2.6%)	6 (2.6%)	0 (0%)	0 (0%)

Outlier analysis for PSO3002:

The tables below include both weeks 16 and 48, and therefore patients that were re-randomization at week 28. The treatment groups are not exclusive, e.g. a patient receiving adalimumab that were randomized to guselkumab at week 28 is included both under adalimumab and adalimumab to guselkumab.

Table 5: Outlier analysis for study PSO3002 through week 48

Treatment Group	Total N		450 < QTcF <= 480 ms		480 < QTcF < 500 ms		QTcF > 500 ms	
	Subj. #	Obs. #	Subj. #	Obs. #	Subj. #	Obs. #	Subj. #	Obs. #
Adalimumab	242	464	7 (2.8%)	7 (1.5%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Adalimumab to Guselkumab	112	221	3 (2.6%)	3 (1.4%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Guselkumab	485	937	18 (3.6%)	21 (2.2%)	1 (0.2%)	1 (0.1%)	0 (0.0%)	0 (0.0%)
Placebo to Guselkumab	80	161	6 (7.1%)	7 (4.3%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)

Table 6: Outlier analysis for change from baseline for study PSO3002 through week 48

Treatment Group	Total N		30 < Δ QTcF \leq 60 ms		Δ QTcF > 60 ms	
	Subj. #	Obs. #	Subj. #	Obs. #	Subj. #	Obs. #
Adalimumab	242	464	5 (1.6%)	5 (1.1%)	0 (0%)	0 (0%)
Adalimumab to Guselkumab	112	221	2 (1.4%)	2 (0.9%)	0 (0%)	0 (0%)
Guselkumab	483	933	22 (3.4%)	27 (2.9%)	0 (0%)	0 (0%)
Placebo to Guselkumab	79	158	4 (3.6%)	4 (2.5%)	0 (0%)	0 (0%)

Thank you for requesting our input into the development of this product under BLA 761061. We welcome more discussion with you now and in the future. Please feel free to contact us via email at cdcrpqt@fda.hhs.gov

Table 7: Highlights of Clinical Pharmacology and Cardiac Safety

<p>Therapeutic dose and exposure</p>	<p><u>Include maximum proposed clinical dosing regimen:</u></p> <ul style="list-style-type: none"> The only proposed clinical dosing regimen for patients with moderate to severe plaque psoriasis is 100 mg administered subcutaneously at Week 0, Week 4, and every 8 weeks thereafter. <p><u>Mean (%CV) C_{max} and AUC at the single maximum proposed clinical dose:</u></p> <ul style="list-style-type: none"> C_{max}: 8.091 µg/mL (45.52%) following a single subcutaneous administration of 100 mg liquid formulation (PFS ^(b)(4) in healthy subjects (Mod2.7.2/Page 32, Study CNTO1959NAP1001) AUC_{inf}: 187.749 µg•day/mL (50.19%) following a single subcutaneous administration of 100 mg liquid formulation (PFS ^(b)(4) in healthy subjects (Mod2.7.2/Page 32, Study CNTO1959NAP1001) <p><u>Mean (%CV) C_{max} and AUC at the steady state with the maximum proposed clinical dosing regimen:</u></p> <ul style="list-style-type: none"> C_{max}: 10.2 µg/mL (41.0%) following 100 mg administered subcutaneously at Week 0, Week 4, and every 8 weeks thereafter in subjects with moderate to severe psoriasis, predicted based on the population pharmacokinetic model developed in subjects with moderate to severe psoriasis (Mod5.3.3.5/Population PK Report) AUC_τ: 206 µg•day/mL (45.5%) following 100 mg administered subcutaneously at Week 0, Week 4, and every 8 weeks thereafter in subjects with moderate to severe psoriasis, predicted based on the population pharmacokinetic model developed in subjects with moderate to severe psoriasis (Mod5.3.3.5/Population PK Report)
<p>Maximum tolerated dose</p>	<p><u>Include if studied or NOAEL dose</u></p> <ul style="list-style-type: none"> The NOAEL dose in cynomolgus monkeys was 50 mg/kg following weekly IV administration for up to 5 weeks or 50 mg/kg following weekly SC administration for up to 24 weeks.

Principal adverse events	<p><u>Include most common adverse events; dose limiting adverse events</u></p> <ul style="list-style-type: none"> Based on the primary safety dataset evaluated in the Summary of Clinical Safety (pooled data from CNTO1959PSO3001 and CNTO1959PSO3002) through the placebo-controlled period, the most common adverse events ($\geq 1\%$) occurring in the guselkumab group were nasopharyngitis, upper respiratory tract infection, headache, arthralgia, hypertension, injection site erythema, pruritis, diarrhea, injection site bruising, back pain, cough, gastroenteritis and fatigue. For most of these common AEs, the frequency of AEs was comparable in the guselkumab and placebo groups. One notable exception was injection site erythema, which was twice as frequent in the guselkumab group as in the placebo group (Mod2.7.4/Sec 2.1.2.1.1). Three adverse drug reactions have been identified for guselkumab: injection site erythema, injection site pain, and gastroenteritis (Mod2.7.4/Sec2.3). No dose-limiting adverse events have been observed. 	
Maximum dose tested	Single Dose	<p><u>Specify dose:</u></p> <ul style="list-style-type: none"> 10 mg/kg intravenous administration in healthy subjects (Mod5.3.3.1/CNTO1959NAP1001/CSR)
	Multiple Dose	<p><u>Specify dosing interval and duration:</u></p> <ul style="list-style-type: none"> 200 mg administered subcutaneously at Week 0, Week 4, and every 8 weeks thereafter in subjects with rheumatoid arthritis (Mod5.3.5.4/CNTO1275ARA2001/CSR)
Exposures Achieved at Maximum Tested Dose	Single Dose	<p><u>Mean (%CV) C_{max} and AUC:</u></p> <ul style="list-style-type: none"> C_{max}: 197.46 $\mu\text{g/mL}$ (17.01%) following a single intravenous administration of 10 mg/kg in healthy subjects (Mod2.7.2/Page 29, Study CNTO1959PSO1001, Part 1) AUC_{inf}: 2214.52 $\mu\text{g}\cdot\text{day/mL}$ (15.59%) following a single intravenous administration of 10 mg/kg in healthy subjects (Mod2.7.2/Page 29, Study CNTO1959PSO1001, Part 1)
	Multiple Dose	<p><u>Mean (%CV) C_{max} and AUC:</u></p> <ul style="list-style-type: none"> Since a sparse PK sampling scheme was used in subjects with rheumatoid arthritis who received 200 mg guselkumab administered subcutaneously at Week 0, Week 4, and every 8 weeks thereafter, the observed C_{max} and AUC_{τ} could not be obtained. Thus, C_{max} and AUC_{τ} values were calculated based on <i>post hoc</i> PK parameters obtained from the population PK model developed in subjects with moderate to

		<p>severe psoriasis using data from the Phase 2 and 3 studies (Mod5.3.3.5/Population PK Report).</p> <ul style="list-style-type: none"> • C_{max}: 20.4 $\mu\text{g/mL}$ (41.0%) following 200 mg administered subcutaneously at Week 0, Week 4, and every 8 weeks thereafter, calculated based on <i>post hoc</i> PK parameters obtained from the population PK model developed in subjects with moderate to severe psoriasis (Mod5.3.3.5/Population PK Report). • AUC_t: 412 $\mu\text{g}\cdot\text{day/mL}$ (45.5%) following 100 mg administered subcutaneously at Week 0, Week 4, and every 8 weeks thereafter, calculated based on <i>post hoc</i> PK parameters obtained from the population PK model developed in subjects with moderate to severe psoriasis (Mod5.3.3.5/Population PK Report). • Since the median body weight in the subjects with rheumatoid arthritis is smaller than that in the subjects with moderate to severe psoriasis, the C_{max} and AUC following the same dose regimen in subjects with rheumatoid arthritis was likely slightly higher.
Range of linear PK	<p><u>Specify dosing regimen:</u></p> <ul style="list-style-type: none"> • Following single intravenous administration in healthy subjects, approximate dose-proportionality was observed from 0.03 to 10 mg/kg (Mod.2.7.2/Page 55, Study CNTO 1959PSO1001, Part 1). • Following single subcutaneous administration in subjects with moderate to severe psoriasis, approximate dose-proportionality was observed from 10 mg to 300 mg (Mod2.7.2/Page 55, Study CNTO1959PSO1001, Part 2, and CNTO1959PSO1002). • Following multiple-dose subcutaneous administration in subjects with moderate to severe psoriasis (q8w or q12w), approximate dose-proportionality was observed at dose levels ranging from 15 to 200 mg (Mod2.7.2/Page 57, Study CNTO1959PSO2001). 	

Accumulation at steady state	<u>Mean (%CV); specify dosing regimen:</u> <ul style="list-style-type: none"> Following 100 mg administered subcutaneously at Week 0, Week 4, and every 8 weeks thereafter, the accumulation ratio is calculated to be 1.13 (5.4%) based on the population pharmacokinetic model developed in subjects with moderate to severe psoriasis (Mod5.3.3.5/Population PK Report). 	
Metabolites	<u>Include listing of all metabolites and activity:</u> <ul style="list-style-type: none"> As a fully human IgG1λ monoclonal antibody, guselkumab is expected to be metabolized in the same manner as any other endogenous IgG, ie, degraded into small peptides and amino acids via catabolic pathways. 	
Absorption	Absolute/Relative Bioavailability	<u>Mean (%CV):</u> <ul style="list-style-type: none"> 48.7% (50.2%) in healthy subjects receiving a single 100 mg subcutaneous administration of liquid formulation (PFS ^(b)₍₄₎) (Mod5.3.3.1/CNTO1959NAP1001 CSR)
	Tmax	<u>Median (range) for parent:</u> <ul style="list-style-type: none"> 3.2 days (2.0, 7.0) in subjects with moderate to severe psoriasis following a single 100 mg subcutaneous administration (Mod5.3.3.1/CNTO1959PSO1001 CSR) <u>Median (range) for metabolites:</u> <ul style="list-style-type: none"> not applicable to monoclonal antibodies like guselkumab
Distribution	Vz/F	<u>Mean (%CV):</u> <ul style="list-style-type: none"> 250.76 mL/kg (44.55%) in subjects with moderate to severe psoriasis following a single 100 mg subcutaneous administration (Mod2.7.2/ Page 37, Study CNTO1959PSO1001, Part 2)
	% bound	<u>Mean (%CV):</u> <ul style="list-style-type: none"> not applicable to monoclonal antibodies like guselkumab
Elimination	Route	<u>Primary route; percent dose eliminated</u> <u>Other routes</u> <ul style="list-style-type: none"> As a fully human IgG1λ monoclonal antibody, guselkumab is expected to be metabolized in the same manner as any other endogenous IgG, ie, degraded into small peptides and amino acids via catabolic pathways.
	Terminal t $\frac{1}{2}$	<u>Mean (%CV) for parent:</u> <ul style="list-style-type: none"> 15.89 day (20.79%) in subjects with moderate to severe psoriasis following a single 100 mg subcutaneous administration (Mod2.7.2/Page 37, Study CNTO1959PSO1001. Part 2)

		<p><u>Mean (%CV) for metabolites:</u></p> <ul style="list-style-type: none"> not applicable to monoclonal antibody like guselkumab
	CL/F	<p><u>Mean (%CV):</u> 11.29 mL/day/kg (42.67%) in subjects with moderate to severe psoriasis following a single 100 mg subcutaneous administration (Mod2.7.2/Page 37, Study CNTO1959PSO1001, Part 2)</p>
Intrinsic Factors	Age	<p><u>Specify mean changes in C_{max} and AUC_τ:</u></p> <ul style="list-style-type: none"> Individual C_{max} and AUC_τ values were calculated based on <i>post hoc</i> PK parameters obtained from the population PK model developed in subjects with moderate to severe psoriasis using data from the Phase 2 and 3 studies. These parameters were summarized based on age categories as follows (Mod5.3.3.5/ Population PK Report). <p>Compared to subjects ≤65 yr, elderly subjects have similar steady-state C_{max} and AUC_τ, respectively.</p> <p>≤65 yr: C_{max}: 10.2 µg/mL (41.5%) AUC_τ: 206 µg/mL•d (45.8%)</p> <p>>65 yr: C_{max}: 10.1 µg/mL (30.5%) AUC_τ: 210 µg/mL•d (39.5%)</p>
	Sex	<p><u>Specify mean changes in C_{max} and AUC_τ:</u></p> <ul style="list-style-type: none"> Individual C_{max} and AUC_τ values were calculated based on <i>post hoc</i> PK parameters obtained from the population PK model developed in subjects with moderate to severe psoriasis using data from the Phase 2 and 3 studies. These parameters were summarized based on sex as follows (Mod5.3.3.5/Population PK Report). <p>Compared to male subjects, female subjects have similar steady-state C_{max} and AUC_τ, respectively.</p> <p>Male: C_{max}: 9.93 µg/mL (43.5%) AUC_τ: 202 µg/mL•d (46.3%)</p>

		<p>Female: C_{max}: 10.8 $\mu\text{g/mL}$ (34.7%) $\text{AUC}\tau$: 217 $\mu\text{g/mL}\cdot\text{d}$ (43.4%)</p>
	Race	<p><u>Specify mean changes in C_{max} and $\text{AUC}\tau$:</u></p> <ul style="list-style-type: none"> Individual C_{max} and $\text{AUC}\tau$ values were calculated based on <i>post hoc</i> PK parameters obtained from the population PK model developed in subjects with moderate to severe psoriasis using data from the Phase 2 and 3 studies. These parameters were summarized in different race categories as follows (Mod5.3.3.5/ Population PK Report) <p>Compared to White subjects, the mean steady-state C_{max} and $\text{AUC}\tau$ in Black subjects increased by 7.5% and 20.7%, respectively. However, the sample size for black subjects is very small and only accounted for <2% of the total subjects in the analysis dataset. In Asian subjects, the steady-state C_{max} and $\text{AUC}\tau$ were similar to those, respectively, in White subjects.</p> <p>White: C_{max}: 10.2 $\mu\text{g/mL}$ (42.7%) $\text{AUC}\tau$: 208 $\mu\text{g/mL}\cdot\text{d}$ (46.4%)</p> <p>Black: C_{max}: 9.44 $\mu\text{g/mL}$ (37.2%) $\text{AUC}\tau$: 165 $\mu\text{g/mL}\cdot\text{d}$ (45.4%)</p> <p>Asian: C_{max}: 10.4 $\mu\text{g/mL}$ (29.1%) $\text{AUC}\tau$: 200 $\mu\text{g/mL}\cdot\text{d}$ (36.6%)</p>
	Hepatic & Renal Impairment	<p><u>Specify mean changes in C_{max} and $\text{AUC}\tau$:</u></p> <ul style="list-style-type: none"> No specific studies have been conducted to determine the effects of hepatic or renal impairment on the pharmacokinetics of guselkumab.

Extrinsic Factors	Drug interactions	<p><u>Include listing of studied DDI studies with mean changes in C_{max} and AUC:</u></p> <ul style="list-style-type: none"> An <i>in vitro</i> study indicated that IL-23 did not alter the expression or activity of multiple cytochrome (CYP) P450 enzymes (CYP1A2, 2B6, 2C9, 2C19, 2D6, and 3A4). A Phase 1 clinical study (CNTO1959PSO1003) in subjects with moderate to severe psoriasis to evaluate whether blocking IL-23 with guselkumab for the treatment of psoriasis would alter the metabolism of probe substrates metabolized by CYP450 isozymes (midazolam [CYP3A4], warfarin [CYP2C9], omeprazole [CYP2C19], dextromethorphan [CYP2D6], and caffeine [CYP1A2], has just been completed. The results are being analyzed and the Clinical Study Report will be provided with the 120-day safety update.
	Food Effects	<p><u>Specify mean changes in C_{max} and AUC and meal type (i.e., high-fat, standard, low-fat):</u></p> <ul style="list-style-type: none"> Guselkumab is administrated subcutaneously; therefore, a food effect is not considered relevant.
Expected High Clinical Exposure Scenario	<p><u>Describe worst case scenario and expected fold-change in C_{max} and AUC. The increase in exposure should be covered by the supra-therapeutic dose.:</u></p> <ul style="list-style-type: none"> Following single intravenous administration of 10 mg/kg, mean C_{max} and AUC_{inf} were 197.46 µg/mL and 2214.52 µg•day/mL, respectively, which are 18.4-fold and 9.8-fold higher than those following the recommended clinical dose at steady state, ie, 100 mg at Weeks 0, 4, and followed by q8w via subcutaneous administration. Guselkumab is expected to be well-tolerated with no C_{max}-related acute toxicity. 	
Preclinical Cardiac Safety	<p>In vitro, the hERG assay which is standardly conducted for small molecule drugs, was not considered appropriate for guselkumab since large molecule drugs such as guselkumab have low/no potential to interact with the intra- and extracellular domains of the hERG channel (Vargus et al, 2008)³. Guselkumab was, however, evaluated in-vitro in non-GLP and GLP tissue cross-reactivity studies using human and cynomolgus monkey (cross-reactive toxicology species) tissues to assess the potential of guselkumab to bind to unintended targets. Results revealed cytoplasmic staining to both skeletal and cardiac myocytes; however, the in vitro cytoplasmic staining of myocytes was not considered to be relevant to in vivo administration because antibodies are too large to diffuse across plasma membranes and are unable to gain access to the intracellular environment.</p>	

	<p>In vivo, potential CV risk associated with guselkumab administration was evaluated in the 5-week subchronic/24-week chronic repeated dose toxicology study, and separately in a CV safety pharmacology study, both in the cynomolgus monkey. There were no treatment-related adverse effects on safety pharmacology parameters in cynomolgus monkeys administered ≤ 50 mg/kg/week guselkumab IV for 5 weeks or SC for up to 24 weeks. Results from the CV study indicated no adverse effects of guselkumab on any of the CV parameters evaluated (systolic, diastolic and mean arterial pressure; electrocardiograms [PR, QRS, RR, QT, and QTcB (Bazett's)]; heart rate; body temperature). There was no cytoplasmic staining of myocytes detected by IHC when guselkumab was administered systemically to monkeys.</p> <p>Published peer reviewed literature indicates a potential role for inhibition of IL-23 (and IL-17) in slowing or reversing coronary artery disease (CAD) progression (eg, Abbas et al, 2015),¹ although there is some conflicting literature that indicates a beneficial role for presence of IL-23 in CAD (eg, Savvatis et al, 2014).²</p> <p>Taken together, the weight of the preclinical evidence does not support an increased risk of CV events in the setting of IL-23 blockade with guselkumab (Mod2.4/NCO and Mod2.6.7/Tox Tabulated Summary).</p>
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Clinical Cardiac Safety	<p><u>Describe total number of clinical trials and number of subjects at different drug exposure levels. Summarize cardiac safety events per ICH E14 guidance (e.g., QT prolongation, syncope, seizures, ventricular arrhythmias, ventricular tachycardia, ventricular fibrillation, flutter, torsade de pointes, or sudden deaths).</u></p> <ul style="list-style-type: none"> • A summary of the 6 core psoriasis studies, including the number of subjects in each study exposed to guselkumab and the corresponding dose levels, is provided in Table 2 (also presented in the Summary of Clinical Safety, Mod2.7.4/Sec 1.1.1.1). Adverse Events (AEs) after Week 16 treatment for randomized subjects in CNTO1959PSO3003 and after exposure to study agent at Week 0 (control or guselkumab) for the other 5 studies were searched for all of the AE preferred terms included in the Standard MedDRA Query (SMQ) terms for Torsades de pointes/QT prolongation (provided in attached Table 3). These searches yielded a total of 2 AEs of syncope, which are summarized in Table 4. These events, both from the CNTO1959PSO3002 study, occurred in subjects who were randomized to placebo after they crossed over to guselkumab. One of these events was serious, and occurred in a 44 year-old woman with a history of psoriasis, psoriatic arthritis, and migraines who had a headache and fainted. She was hospitalized, and her evaluation included a head CT, brain MRI and EEG, which were all unremarkable. She was treated with sumatriptan, Axotal, and valproate semisodium, and was discharged 3 days later with diagnoses of headache and syncope. The second event was a nonserious event that occurred in a 35 year-old woman with no reported medical history other than psoriasis. The event was reported as “swoon”, characterized as mild by the investigator and occurred on the same date as an AE of diarrhea. No medical records were available for this event. • A thorough QT study was not performed for guselkumab; however, the safety assessment for guselkumab included collection of sufficient ECG data to exclude a clinically important effect on cardiac electrical activity, including the QT interval. There was no evidence for any clinically meaningful changes from baseline in ECG interval values in the pooled safety analysis set (CNTO1959PSO3001 and CNTO1959PSO3002), nor in the other core psoriasis studies or the completed studies in other indications or populations (Mod2.7.4/Sec4.2). In addition, across the clinical development program, there was no evidence for treatment-related changes in BP or pulse rate in subjects exposed to guselkumab (Mod2.7.4/Sec4.1).
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This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

LARS JOHANNESSEN
02/10/2017

CHRISTINE E GARNETT
02/10/2017

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		
BLA# 761061	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: Guselkumab Dosage Form: Injection Strengths: 100 mg/mL		
Applicant: Janssen Biotech, Inc. Agent for Applicant (if applicable): N/A		
Date of Application: 11/16/2016 Date of Receipt: 11/16/2016 Date clock started after Unacceptable for Filing (UN): N/A		
PDUFA Goal Date: 7/16/2016	Action Goal Date (if different):	
Filing Date: 1/15/2017	Date of Filing Meeting: 12/15/2016	
Chemical Classification (original NDAs only) : <input checked="" 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: For the treatment of adult patients with moderate-to-severe plaque psoriasis who are candidates for systemic therapy or phototherapy		
Type of Original NDA: AND (if applicable) Type of NDA Supplement:	<input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2) <input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2)	
<i>If 505(b)(2)NDA/NDA Supplement: Draft the “505(b)(2) Assessment” review found at:</i> http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027499 .		

Type of BLA	<input checked="" type="checkbox"/> 351(a) <input type="checkbox"/> 351(k)
<i>If 351(k), notify the OND Therapeutic Biologics and Biosimilars Team</i>	
Review Classification:	<input type="checkbox"/> Standard <input checked="" type="checkbox"/> Priority
<i>The application will be a priority review if:</i>	<input type="checkbox"/> Pediatric WR
<ul style="list-style-type: none"><i>A complete response to a pediatric Written Request (WR) was included (a partial response to a WR that is sufficient to change the labeling should also be a priority review – check with DPMH)</i>	<input type="checkbox"/> QIDP
<ul style="list-style-type: none"><i>The product is a Qualified Infectious Disease Product (QIDP)</i>	<input checked="" type="checkbox"/> Tropical Disease Priority Review Voucher
<ul style="list-style-type: none"><i>A Tropical Disease Priority Review Voucher was submitted</i>	<input type="checkbox"/> Pediatric Rare Disease Priority Review Voucher
<ul style="list-style-type: none"><i>A Pediatric Rare Disease Priority Review Voucher was submitted</i>	
Resubmission after withdrawal? <input type="checkbox"/>	Resubmission after refuse to file? <input type="checkbox"/>
Part 3 Combination Product? <input checked="" type="checkbox"/>	<input type="checkbox"/> Convenience kit/Co-package
<i>If yes, contact the Office of Combination Products (OCP) and copy them on all Inter-Center consults</i>	<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"/> PMC response
<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"/> PMR response:
<input type="checkbox"/> Rolling Review	<input type="checkbox"/> FDAAA [505(o)]
<input type="checkbox"/> Orphan Designation	<input type="checkbox"/> PREA deferred pediatric studies (FDCA Section 505B)
<input type="checkbox"/> Rx-to-OTC switch, Full	<input type="checkbox"/> Accelerated approval confirmatory studies (21 CFR 314.510/21 CFR 601.41)
<input type="checkbox"/> Rx-to-OTC switch, Partial	<input type="checkbox"/> Animal rule postmarketing studies to verify clinical benefit and safety (21 CFR 314.610/21 CFR 601.42)
<input type="checkbox"/> Direct-to-OTC	
Other:	

Collaborative Review Division (if OTC product):

List referenced IND Number(s): 105004

Goal Dates/Product Names/Classification Properties	YES	NO	NA	Comment
PDUFA/BsUFA and Action Goal dates correct in the electronic archive?	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
<i>If no, ask the document room staff to correct them immediately. These are the dates used for calculating inspection dates.</i>				
Are the established/proper and applicant names correct in electronic archive?	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
<i>If no, ask the document room staff to make the corrections. Also, ask the document room staff to add the established/proper name</i>				

<i>to the supporting IND(s) if not already entered into electronic archive.</i>				
Is the review priority (S or P) and all appropriate classifications/properties entered into tracking system (e.g., chemical classification, combination product classification, orphan drug)? <i>Check the New Application and New Supplement Notification Checklists for a list of all classifications/properties at:</i> http://inside.fda.gov:9003/CDER/OfficeofBusinessProcessSupport/ucm163969.htm <i>If no, ask the document room staff to make the appropriate entries.</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Application Integrity Policy	YES	NO	NA	Comment
Is the application affected by the Application Integrity Policy (AIP)? <i>Check the AIP list at:</i> http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm	<input type="checkbox"/>	<input checked="" type="checkbox"/>		
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"/>		
User Fees	YES	NO	NA	Comment
Is Form 3397 (User Fee Cover Sheet)/Form 3792 (Biosimilar User Fee Cover Sheet) included with authorized signature?	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
<u>User Fee Status</u> <i>If a user fee is required and it has not been paid (and it is not exempted or waived), the application is unacceptable for filing following a 5-day grace period from receipt. Review stops. Contact the User Fee Staff. If appropriate, send UN letter.</i>	Payment for this application (<i>check daily email from UserFeeAR@fda.hhs.gov</i>): <input checked="" type="checkbox"/> Paid <input type="checkbox"/> Exempt (orphan, government) <input type="checkbox"/> Waived (e.g., small business, public health) <input type="checkbox"/> Not required			
<i>If the firm is in arrears for other fees (regardless of whether a user fee has been paid for this application), the application is unacceptable for filing (5-day grace period does not apply). Review stops. 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> http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM079320.pdf	Has the user fee bundling policy been appropriately applied? <i>If no, or you are not sure, consult the User Fee Staff.</i> <input checked="" type="checkbox"/> Yes <input type="checkbox"/> No			
505(b)(2) (NDAs/NDA Efficacy Supplements only)	YES	NO	NA	Comment
Is the application a 505(b)(2) NDA? (<i>Check the 356h form,</i>	<input type="checkbox"/>	<input type="checkbox"/>		

cover letter, and annotated labeling). If yes , answer the bulleted questions below:					
• Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?		<input type="checkbox"/>	<input type="checkbox"/>		
• Is the application for a duplicate of a listed drug whose only difference is that the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action is less than that of the reference listed drug (RLD)? [see 21 CFR 314.54(b)(1)].		<input type="checkbox"/>	<input type="checkbox"/>		
• 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)]?		<input type="checkbox"/>	<input type="checkbox"/>		
<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>					
• Is there unexpired exclusivity on another listed drug product containing the same active moiety (e.g., 5-year, 3-year, orphan, or pediatric exclusivity)?		<input type="checkbox"/>	<input type="checkbox"/>		
Check the Electronic Orange Book at: http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm					
If yes , please list below:					
Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration		
<i>If there is unexpired, 5-year exclusivity remaining on another listed drug product containing the same active moiety, a 505(b)(2) application cannot be submitted until the period of exclusivity expires (unless the applicant provides paragraph IV patent certification; then an application can be submitted four years after the date of approval.) Pediatric exclusivity will extend both of the timeframes in this provision by 6 months. 21 CFR 314.108(b)(2). Unexpired orphan or 3-year exclusivity may block the approval but not the submission of a 505(b)(2) application.</i>					
Exclusivity	YES	NO	NA	Comment	
Does another product (same active moiety) have orphan exclusivity for the same indication? Check the Orphan Drug Designations and Approvals list at: http://www.accessdata.fda.gov/scripts/opdlisting/oopd/index.cfm	<input type="checkbox"/>	<input checked="" type="checkbox"/>			
If another product has orphan exclusivity , is the product considered to be the same product according to the orphan drug definition of sameness [see 21 CFR 316.3(b)(14)]?	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>		
<i>If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy</i>					
NDAs/NDA efficacy supplements only: Has the applicant requested 5-year or 3-year Waxman-Hatch exclusivity?	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>		
If yes , # years requested:					
<i>Note: An applicant can receive exclusivity without requesting it;</i>					

<i>therefore, requesting exclusivity is not required.</i>				
NDAs only: Is the proposed product a single enantiomer of a racemic drug previously approved for a different therapeutic use?	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
If yes, did the applicant: (a) elect to have the single enantiomer (contained as an active ingredient) not be considered the same active ingredient as that contained in an already approved racemic drug, and/or (b): request exclusivity pursuant to section 505(u) of the Act (per FDAAA Section 1113)? <i>If yes, contact the Orange Book Staff (CDER-Orange Book Staff).</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
BLAs only: Has the applicant requested 12-year exclusivity under section 351(k)(7) of the PHS Act? <i>If yes, notify Marlene Schultz-DePalo, 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				
<i>Do not check mixed submission if the only electronic component is the content of labeling (COL).</i>	<input type="checkbox"/> All paper (except for COL) <input checked="" type="checkbox"/> All electronic <input type="checkbox"/> Mixed (paper/electronic) <input checked="" type="checkbox"/> CTD <input type="checkbox"/> Non-CTD <input type="checkbox"/> Mixed (CTD/non-CTD)			
If mixed (paper/electronic) submission, which parts of the application are submitted in electronic format?				
Overall Format/Content	YES	NO	NA	Comment
If electronic submission, does it follow the eCTD guidance? ¹ If not, explain (e.g., waiver granted).	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Index: Does the submission contain an accurate comprehensive index?	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
Is the submission complete as required under 21 CFR 314.50 (NDAs/NDA efficacy supplements) or under 21 CFR 601.2 (BLAs/BLA efficacy supplements) including: <input checked="" type="checkbox"/> legible	<input checked="" type="checkbox"/>	<input type="checkbox"/>		

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

<input checked="" type="checkbox"/> English (or translated into English) <input checked="" type="checkbox"/> pagination <input checked="" type="checkbox"/> navigable hyperlinks (electronic submissions only)				
If no, explain.				
BLAs only: Companion application received if a shared or divided manufacturing arrangement?	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
If yes, BLA #				
Forms and Certifications				
<i>Electronic forms and certifications with electronic signatures (scanned, digital, or electronic – similar to DARRTS, e.g., /s/) are acceptable. Otherwise, paper forms and certifications with hand-written signatures must be included. Forms include: user fee cover sheet (3397/3792), application form (356h), patent information (3542a), financial disclosure (3454/3455), and clinical trials (3674); Certifications include: debarment certification, patent certification(s), field copy certification, and pediatric certification.</i>				
Application Form	YES	NO	NA	Comment
Is form FDA 356h included with authorized signature per 21 CFR 314.50(a)?	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
<i>If foreign applicant, a U.S. agent must sign the form [see 21 CFR 314.50(a)(5)].</i>				
Are all establishments and their registration numbers listed on the form/attached to the form?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Patent Information (NDAs/NDA efficacy supplements only)	YES	NO	NA	Comment
Is patent information submitted on form FDA 3542a per 21 CFR 314.53(c)?	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
Financial Disclosure	YES	NO	NA	Comment
Are financial disclosure forms FDA 3454 and/or 3455 included with authorized signature per 21 CFR 54.4(a)(1) and (3)?	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
<i>Forms must be signed by the APPLICANT, not an Agent [see 21 CFR 54.2(g)].</i>				
<i>Note: Financial disclosure is required for bioequivalence studies that are the basis for approval.</i>				
Clinical Trials Database	YES	NO	NA	Comment
Is form FDA 3674 included with authorized signature?	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
<i>If yes, ensure that the application is also coded with the supporting document category, “Form 3674.”</i>				
<i>If no, ensure that language requesting submission of the form is included in the acknowledgement letter sent to the applicant</i>				

Debarment Certification	YES	NO	NA	Comment
<p>Is a correctly worded Debarment Certification included with authorized signature?</p> <p><i>Certification is not required for supplements if submitted in the original application; If foreign applicant, <u>both</u> the applicant and the U.S. Agent must sign the certification [per Guidance for Industry: Submitting Debarment Certifications].</i></p> <p><i>Note: Debarment Certification should use wording in FD&C Act Section 306(k)(1) i.e., “[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application.” Applicant may not use wording such as, “To the best of my knowledge...”</i></p>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Field Copy Certification (NDAs/NDA efficacy supplements only)	YES	NO	NA	Comment
<p>For paper submissions only: Is a Field Copy Certification (that it is a true copy of the CMC technical section) included?</p> <p><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></p> <p><i>If maroon field copy jackets from foreign applicants are received, return them to CDR for delivery to the appropriate field office.</i></p>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
Controlled Substance/Product with Abuse Potential	YES	NO	NA	Comment
<p><u>For NMEs:</u> 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><u>For non-NMEs:</u> <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><u>PREA</u></p> <p>Does the application trigger PREA?</p> <p><i>If yes, notify PeRC@fda.hhs.gov to schedule required PeRC meeting²</i></p>	<input checked="" type="checkbox"/>	<input type="checkbox"/>		

2

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

Version: 9/29/2016

7

<i>Note: NDAs/BLAs/efficacy supplements for new active ingredients (including new fixed combinations), new indications, new dosage forms, new dosing regimens, or new routes of administration trigger PREA. All waiver & deferral requests, pediatric plans, and pediatric assessment studies must be reviewed by PeRC prior to approval of the application/supplement.</i>				
If the application triggers PREA , is there an agreed Initial Pediatric Study Plan (iPSP)? <i>If no, may be an RTF issue - contact DPMH for advice.</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
If required by the agreed iPSP , are the pediatric studies outlined in the agreed iPSP completed and included in the application? <i>If no, may be an RTF issue - contact DPMH for advice.</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	Waiver for subjects 0 to less than 6 years of age Deferral in subjects 6 to less than 18 years of age until such time as adult safety experience can be evaluated.
<u>BPCA:</u> Is this submission a complete response to a pediatric Written Request? <i>If yes, notify Pediatric Exclusivity Board RPM (pediatric exclusivity determination is required³)</i>	<input type="checkbox"/>	<input checked="" type="checkbox"/>		
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"/>	
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"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>
	<input checked="" type="checkbox"/> Package Insert (Prescribing Information)(PI)	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>
	<input type="checkbox"/> Patient Package Insert (PPI)	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>
	<input checked="" type="checkbox"/> Instructions for Use (IFU)	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>
	<input checked="" type="checkbox"/> Medication Guide (MedGuide)	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>
	<input checked="" type="checkbox"/> Carton labeling	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>
	<input checked="" type="checkbox"/> Immediate container labels	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>
	<input type="checkbox"/> Diluent labeling	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>
	<input type="checkbox"/> Other (specify)	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>
	YES	NO	NA	Comment
Is Electronic Content of Labeling (COL) submitted in SPL	<input checked="" type="checkbox"/>	<input type="checkbox"/>		

3

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

format?				
<i>If no, request applicant to submit SPL before the filing date.</i>				
Is the PI submitted in Physician Labeling Rule (PLR) format? ⁴	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
If PI not submitted in PLR format , was a waiver or deferral requested before the application was received or in the submission? If requested before application was submitted , what is the status of the request?	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
<i>If no waiver or deferral, request applicant to submit labeling in PLR format before the filing date.</i>				
For applications submitted on or after June 30, 2015: Is the PI submitted in Pregnancy and Lactation Labeling Rule (PLLR) format?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
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 type="checkbox"/>	<input type="checkbox"/>	
For applications submitted on or after June 30, 2015: If PI not submitted in PLLR format , was a waiver or deferral requested before the application was received or in the submission? If requested before application was submitted , what is the status of the request?	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
<i>If no waiver or deferral, request applicant to submit labeling in PLLR format before the filing date.</i>				
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 checked="" type="checkbox"/>	<input type="checkbox"/>	<input 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"/>	
OTC Labeling	<input type="checkbox"/> Not Applicable			
Check all types of labeling submitted.	<input type="checkbox"/> Outer carton label <input type="checkbox"/> Immediate container label <input type="checkbox"/> Blister card <input type="checkbox"/> Blister backing label <input type="checkbox"/> Consumer Information Leaflet (CIL) <input type="checkbox"/> Physician sample			

4

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

	<input type="checkbox"/> Consumer sample <input type="checkbox"/> Other (specify)			
	YES	NO	NA	Comment
Is electronic content of labeling (COL) submitted? <i>If no, request in 74-day letter.</i>	<input type="checkbox"/>	<input type="checkbox"/>		
Are annotated specifications submitted for all stock keeping units (SKUs)? <i>If no, request in 74-day letter.</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
If representative labeling is submitted, are all represented SKUs defined? <i>If no, request in 74-day letter.</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
All labeling/packaging sent to OSE/DMEPA?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Other Consults	YES	NO	NA	Comment
Are additional consults needed? (e.g., IFU to CDRH; QT study report to QT Interdisciplinary Review Team) <i>If yes, specify consult(s) and date(s) sent:</i> DCRP – 12/17/16 OSE – HF: 11/22/16 Maternal Health: 11/18/16 QT-IRT: 11/21/16 COA: 11/21/16 DPP: 11/21/16 CDRH GHDB: 11/17/16 CDRH OC: 11/17/16	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Meeting Minutes/SPAs	YES	NO	NA	Comment
End-of Phase 2 meeting(s)? Date(s): 4/9/2014	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
Pre-NDA/Pre-BLA/Pre-Supplement meeting(s)? Date(s): 4/27/16	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
Any Special Protocol Assessments (SPAs)? Date(s):	<input type="checkbox"/>	<input checked="" type="checkbox"/>		

ATTACHMENT

MEMO OF FILING MEETING

DATE: December 15, 2016

BACKGROUND:

Janssen Biotech, Inc., has submitted BLA 761061 for guselkumab, a human IgG1 λ monoclonal antibody that binds to human IL-23. The proposed indication is treatment of moderate to severe plaque psoriasis in patients who are candidates for systemic therapy or phototherapy. Guselkumab was evaluated under IND 105004.

This BLA has been designated for priority review under a tropical disease voucher

REVIEW TEAM:

Discipline/Organization	Names		Present at filing meeting? (Y or N)
Regulatory Project Management	RPM:	Matthew White	Y
	CPMS/TL:	Barbara Gould	Y
Cross-Discipline Team Leader (CDTL)	Gordana Diglisic		Y
Division Director/Deputy	Kendall A. Marcus/Jill Lindstrom		Y/Y
Office Director/Deputy	Julie Beitz/Amy Egan		Y/Y
Clinical	Reviewer:	Melinda McCord/Kevin Clark	Y/Y
	TL:	Gordana Diglisic	Y
Clinical Pharmacology	Reviewer:	Anand Balakrishnan	Y
	TL:	Yow-Ming Wang	Y
• Pharmacometrics	Reviewer:	Simbarashe Peter Zvada/Jeffry Florian	Y/Y
Biostatistics	Reviewer:	Matthew Guerra	Y
	TL:	Mohamed Alosh	Y
Nonclinical (Pharmacology/Toxicology)	Reviewer:	Renqin Duan	Y
	TL:	Barbara Hill	Y
Product Quality (CMC) Review Team:	ATL:	Joanna Zhou	Y

	RBPM:	Kelly Ballard	Y
• Drug Substance	Reviewer:	Willie Wilson	Y
• Drug Product	Reviewer:	Willie Wilson	Y
• Microbiology	Reviewer:	Candace Gomez-Broughton Bo Chi	Y/Y
• Facility	Reviewer:	Viviana Matta	N
• Labeling (BLAs only)	Reviewer:	Jibril Abdus-Samad	N
OMP/OMPI/DMPP (MedGuide, PPI, IFU)	Reviewer:	Rowe Medina	Y
	TL:	Barbara Fuller	N
OMP/OPDP (PI, PPI, MedGuide, IFU, carton and immediate container labeling)	Reviewer:	Silvia Wanis	Y
	TL:	Matt Falter	Y
OSE/DMEPA (proprietary name, carton/container labeling)	Reviewer:	Carlos Mena-Grillasca	Y
	TL:	Mishale Mistry	Y
OSE/DRISK (REMS)	Reviewer:		
	TL:	Donella Fitzgerald	Y
Other reviewers/disciplines			
• CDRH GHDB	Reviewer:	Keith Marin	N
	TL:	Alan Stevens	N
• CDRH OC	Reviewer:	Christopher Brown	Y
	TL:		Y
• COA	Reviewer:	Yasmin Choudry	Y
	TL:	Selena Daniels	Y
• OSE - DEPI	Reviewer:	Kira Leishear	Y
	TL:	Sukhminder Sandhu	Y
• OSE - DPV	Reviewer:	Jessica Weintraub	Y
	TL:	Vicky Chan	Y
• DPMH	PM	Kerri-Ann Jennings	Y
	Reviewer:	Leyla Sahin	Y

	TL:	Tamara Johnson	Y
• DPP	Reviewer:	John Umhwa	N
	TL:	Javier Muniz	N
• DCRP	Reviewer:	Karen Hicks	N

FILING MEETING DISCUSSION:

<p>GENERAL</p> <ul style="list-style-type: none"> • 505(b)(2) filing issues: <ul style="list-style-type: none"> ○ Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA? ○ Did the applicant provide a scientific “bridge” demonstrating the relationship between the proposed product and the referenced product(s)/published literature? <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>	<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"> • Per reviewers, are all parts in English or English translation? <p>If no, explain:</p>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> • Electronic Submission comments <p>List comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> No comments

<p>CLINICAL</p> <p>Comments: Information request in filing letter</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> Clinical study site(s) inspections(s) needed? <p>If no, explain:</p>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> Advisory Committee Meeting needed? <p>Comments:</p> <p><i>If no, for an NME NDA or original BLA, include the reason. For example:</i></p> <ul style="list-style-type: none"> <i>this drug/biologic is not the first in its class</i> <i>the clinical study design was acceptable</i> <i>the application did not raise significant safety or efficacy issues</i> <i>the application did not raise significant public health questions on the role of the drug/biologic in the diagnosis, cure, mitigation, treatment or prevention of a disease</i> 	<input type="checkbox"/> YES Date if known: <input checked="" type="checkbox"/> NO <input type="checkbox"/> To be determined Reason:
<ul style="list-style-type: none"> If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance? <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO
<p>CONTROLLED SUBSTANCE STAFF</p> <ul style="list-style-type: none"> Abuse Liability/Potential <p>Comments:</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
<p>CLINICAL MICROBIOLOGY</p> <p>Comments:</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

<p>CLINICAL PHARMACOLOGY</p> <p>Comments:</p>	<p><input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE</p> <p><input type="checkbox"/> Review issues for 74-day letter</p>
<p>• Clinical pharmacology study site(s) inspections(s) needed?</p>	<p><input type="checkbox"/> YES <input checked="" type="checkbox"/> NO</p>
<p>BIOSTATISTICS</p> <p>Comments:</p>	<p><input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE</p> <p><input type="checkbox"/> Review issues for 74-day letter</p>
<p>NONCLINICAL (PHARMACOLOGY/TOXICOLOGY)</p> <p>Comments:</p>	<p><input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE</p> <p><input type="checkbox"/> Review issues for 74-day letter</p>
<p>PRODUCT QUALITY (CMC)</p> <p>Comments:</p>	<p><input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE</p> <p><input type="checkbox"/> Review issues for 74-day letter</p>
<p><u>Environmental Assessment</u></p> <p>• Categorical exclusion for environmental assessment (EA) requested?</p> <p>If no, was a complete EA submitted?</p> <p>Comments:</p>	<p><input checked="" type="checkbox"/> YES <input type="checkbox"/> NO</p> <p><input type="checkbox"/> YES <input type="checkbox"/> NO</p>
<p><u>Facility Inspection</u></p> <p>• Establishment(s) ready for inspection?</p> <p>Comments:</p>	<p><input type="checkbox"/> Not Applicable</p> <p><input checked="" type="checkbox"/> YES <input type="checkbox"/> NO</p>

<p><u>Facility/Microbiology Review (BLAs only)</u></p> <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p><u>CMC Labeling Review (BLAs only)</u></p> <p>Comments:</p>	<input type="checkbox"/> Review issues for 74-day letter
<p>CDRH – General Hospital Devices</p> <p>Comments: Information requests in filing letter</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p>APPLICATIONS IN THE PROGRAM (PDUFA V) (NME NDAs/Original BLAs)</p> <ul style="list-style-type: none"> • Were there agreements made at the application’s pre-submission meeting (and documented in the minutes) regarding certain late submission components that could be submitted within 30 days after receipt of the original application? • If so, were the late submission components all submitted within 30 days? 	<input type="checkbox"/> N/A <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> • What late submission components, if any, arrived after 30 days? 	<p>N/A</p>
<ul style="list-style-type: none"> • Was the application otherwise complete upon submission, including those applications where there were no agreements regarding late submission components? 	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> • Is a comprehensive and readily located list of all clinical sites included or referenced in the application? 	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO

<ul style="list-style-type: none">• Is a comprehensive and readily located list of all manufacturing facilities included or referenced in the application?	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
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REGULATORY PROJECT MANAGEMENT	
Signatory Authority: Dr. Julie Beitz	
Date of Mid-Cycle Meeting: February 16, 2017	
REGULATORY CONCLUSIONS/DEFICIENCIES	
<input type="checkbox"/>	The application is unsuitable for filing. Explain why:
<input checked="" type="checkbox"/>	The application, on its face, appears to be suitable for filing. <u>Review Issues:</u> <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. <u>Review Classification:</u> <input type="checkbox"/> Standard Review <input checked="" type="checkbox"/> Priority Review
ACTION ITEMS	
<input 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 checked="" 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 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 ADRA's completed: April 2016

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

/s/

MATTHEW E WHITE

01/12/2017

Signed in DARRTS on behalf of Barbara Gould, CPMS

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

Application: BLA 761061

Application Type: New BLA

Drug Name(s)/Dosage Form(s): Guselkumab injection, 100mg/mL

Applicant: Janssen Biotech, Inc.

Receipt Date: 11/16/2016

Goal Date: 7/16/2016

1. Regulatory History and Applicant's Main Proposals

Guselkumab injection is a human interleukin-23 antagonist indicated for the treatment of adult patients with moderate-to-severe plaque psoriasis who are candidates for systemic therapy or phototherapy

2. Review of the Prescribing Information

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

3. Conclusions/Recommendations

SRPI format deficiencies were identified in the review of this PI. For a list of these deficiencies, see Section 4 of this review.

Recommendation: Conveying the SRPI format deficiencies to the Applicant during labeling discussion.

Selected Requirements of Prescribing Information

4. Selected Requirements of Prescribing Information

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

Highlights

See Appendix for a sample tool illustrating Highlights format.

HIGHLIGHTS GENERAL FORMAT

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

Comment:

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

Comment:

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

Comment:

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

Comment:

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

Comment:

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

Comment:

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

Heading	Required/Optional
• Highlights Heading	Required
• Highlights Limitation Statement	Required

Selected Requirements of Prescribing Information

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

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

Comment:

HIGHLIGHTS DETAILS

Highlights Heading

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

Comment:

Highlights Limitation Statement

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

Comment: *The place holder "TRADENAME" is used in place of the drug name.*

Product Title in Highlights

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

Comment:

Initial U.S. Approval in Highlights

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

Comment:

Boxed Warning (BW) in Highlights

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

Comment:

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

Selected Requirements of Prescribing Information

INFECTIONS and ACUTE HEPATIC FAILURE". If there is more than one warning in the BW title, the word "and" in lower case can separate the warnings. The BW title should be centered.

Comment:

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

Comment:

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

Comment:

Recent Major Changes (RMC) in Highlights

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

Comment:

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

Comment:

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

Comment:

Dosage Forms and Strengths in Highlights

- NO** 19. For a product that has more than one dosage form (e.g., capsules, tablets, injection), bulleted headings should be used.

Comment: *The dosage form is bulleted even though there is only one dosage form.*

Contraindications in Highlights

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

Comment:

Selected Requirements of Prescribing Information

Adverse Reactions in Highlights

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

Comment:

Patient Counseling Information Statement in Highlights

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

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

- **See 17 for PATIENT COUNSELING INFORMATION**

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

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

Comment:

Revision Date in Highlights

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

Comment: *MM/201X used as a placeholder*

Selected Requirements of Prescribing Information

Contents: Table of Contents (TOC)

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

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

Selected Requirements of Prescribing Information

Full Prescribing Information (FPI)

FULL PRESCRIBING INFORMATION: GENERAL FORMAT

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

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

Comment:

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

Comment:

Selected Requirements of Prescribing Information

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

Comment:

FULL PRESCRIBING INFORMATION DETAILS

FPI Heading

- YES** 34. The following heading “**FULL PRESCRIBING INFORMATION**” must be **bolded**, must appear at the beginning of the FPI, and should be in UPPER CASE.

Comment:

BOXED WARNING Section in the FPI

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

Comment:

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

Comment:

CONTRAINDICATIONS Section in the FPI

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

Comment:

ADVERSE REACTIONS Section in the FPI

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

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

Comment:

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

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

Comment:

Selected Requirements of Prescribing Information

PATIENT COUNSELING INFORMATION Section in the FPI

- NO** 40. Must reference any FDA-approved patient labeling in Section 17 (PATIENT COUNSELING INFORMATION). The reference statement should appear at the beginning of Section 17 and include the type(s) of FDA-approved patient labeling (e.g., Patient Information, Instructions for Use, or Medication Guide). Recommended language for the reference statement should include one of the following five verbatim statements that is most applicable:
- Advise the patient to read the FDA-approved patient labeling (Patient Information).
 - Advise the patient to read the FDA-approved patient labeling (Instructions for Use).
 - Advise the patient to read the FDA-approved patient labeling (Patient Information and Instructions for Use).
 - Advise the patient to read the FDA-approved patient labeling (Medication Guide).
 - Advise the patient to read the FDA-approved patient labeling (Medication Guide and Instructions for Use).

Comment: "Advise the patient to read the FDA-approved Medication Guide and Instructions for Use" is used instead of the recommended language shown above.

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

Comment:

Selected Requirements of Prescribing Information

Appendix: Highlights and Table of Contents Format

HIGHLIGHTS OF PRESCRIBING INFORMATION

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

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

WARNING: TITLE OF WARNING

See full prescribing information for complete boxed warning.

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

RECENT MAJOR CHANGES

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

INDICATIONS AND USAGE

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

Limitations of Use: Text (1)

DOSAGE AND ADMINISTRATION

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

DOSAGE FORMS AND STRENGTHS

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

CONTRAINDICATIONS

- Text (4)
- Text (4)

WARNINGS AND PRECAUTIONS

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

ADVERSE REACTIONS

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

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

DRUG INTERACTIONS

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

USE IN SPECIFIC POPULATIONS

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

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

Revised: M/201Y

FULL PRESCRIBING INFORMATION: CONTENTS*

WARNING: TITLE OF WARNING

1 INDICATIONS AND USAGE

2 DOSAGE AND ADMINISTRATION

2.1 Subsection Title

2.2 Subsection Title

3 DOSAGE FORMS AND STRENGTHS

4 CONTRAINDICATIONS

5 WARNINGS AND PRECAUTIONS

5.1 Subsection Title

5.2 Subsection Title

6 ADVERSE REACTIONS

6.1 Clinical Trials Experience

6.2 Immunogenicity

6.2 or 6.3 Postmarketing Experience

7 DRUG INTERACTIONS

7.1 Subsection Title

7.2 Subsection Title

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

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

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

8.4 Pediatric Use

8.5 Geriatric Use

8.6 Subpopulation X

9 DRUG ABUSE AND DEPENDENCE

9.1 Controlled Substance

9.2 Abuse

9.3 Dependence

10 OVERDOSAGE

11 DESCRIPTION

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

12.2 Pharmacodynamics

12.3 Pharmacokinetics

12.4 Microbiology

12.5 Pharmacogenomics

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

13.2 Animal Toxicology and/or Pharmacology

14 CLINICAL STUDIES

14.1 Subsection Title

14.2 Subsection Title

15 REFERENCES

16 HOW SUPPLIED/STORAGE AND HANDLING

17 PATIENT COUNSELING INFORMATION

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

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

/s/

MATTHEW E WHITE

12/02/2016

Signed in DARRTS on behalf of Barbara Gould, CPMS for DDDP