CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

761032Orig1s000

OTHER REVIEW(S)

PMR/PMC Development Template

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

NDA/BLA # Product Name:	BLA 761032 Siliq (brodalumab) injection, 210 mg/ 1.5 mL	
PMR/ Description:	Open-label study to determine PK of a single dos children (6 to < 18 years old) with severe plaque	se of brodalumab in 16 psoriasis.
- PMR Schedule Milestones	: Final Protocol Submission: Study/Trial Completion:	06/2017
	Final Report Submission: Other:	06/2019 06/2019 MM/DD/YYYY

- 1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.
 - Unmet need
 Life-threatening condition
 Long-term data needed
 Only feasible to conduct post-approval
 Prior clinical experience indicates safety
 Small subpopulation affected
 Theoretical concern
 - Other

Moderate to severe psoriasis is uncommon in the pediatric population, representing fewer than 10% of all cases of psoriasis affecting the pediatric population. A waiver is requested for children < 6 years of age based on the fact that necessary studies are impossible or highly impracticable because of the small number of children with the disease. A deferral was requested for children and adolescent's 6 to < 18 years of age. Trials in adult population are ready for approval.

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."

Three studies are proposed to assess the safety and efficacy and dosing of brodalumab in the relevant pediatric population.

- Study 1- 20130249- Phase 1 PK study in children and adolescents.
- Study 2- Phase 3 study in adolescents 12 years to < 18 years.
- Study 3- Phase 3 study in children $^{(b)}_{(4)}$ years to < 12 years.

The designs of the studies are to evaluate PK in children and adolescents to extrapolate efficacy from the adult population. The Phase 3 designs are to provide step-wise approach to safety in treating the pediatric population.

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

<u>Clinical trial</u>: 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 single PK study in children will be completed before the initiation of 2 Phase 3 clinical trials to evaluate safety in a step-wise approach in adolescent to children as described above.

	Required
	Observational pharmacoepidemiologic study
	Registry studies
	Primary safety study or clinical trial
	Thereway O 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
	(provide explenation)
	(provide explanation)
	Meta-analysis or pooled analysis of previous studies/clinical trials
	Immunogenicity as a marker of safety
	Other (provide explanation)
	Agreed upon:
	Ouality 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 <u>each</u> PMR/PMC in the Action Package.

NDA/BLA # BL Product Name: Sili	BLA 761032 Siliq (brodalumab) injection, 210 mg/ 1.5 mL	
PMR/ Description:		
Do	uble-blind, active comparator-controlled, mu	ticenter study with
< 1	8 years old) with severe plaque psoriasis.	In addrescent subjects (12 to
PMR Schedule Milestones:	Final Protocol Submission:	04/2019
	Study/Trial Completion:	01/2024
	Final Report Submission:	06/2024
	Other:	MM/DD/YYYY

- 1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.
 - Unmet need
 Life-threatening condition
 Long-term data needed
 Only feasible to conduct post-approval
 Prior clinical experience indicates safety
 Small subpopulation affected
 Theoretical concern
 - Other

Moderate to severe psoriasis is uncommon in the pediatric population, representing fewer than 10% of all cases of psoriasis affecting the pediatric population. A waiver is requested for children < 6 years of age based on the fact that necessary studies are impossible or highly impracticable because of the small number of children with the disease. A deferral was requested for children and adolescent's 6 to < 18 years of age. Trials in adults are ready for approval.

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."

Three studies are proposed to assess the safety and efficacy and dosing of brodalumab in the relevant pediatric population.

- Study 1- 20130249- Phase 1 PK study in children and adolescents.
- Study 2- Phase 3 study in adolescents 12 years to < 18 years.
- Study 3- Phase 3 study in children $^{(b)}_{(4)}$ years to < 12 years.

The Phase 3 designs are to provide step-wise approach to safety in treating the pediatric population.

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

<u>Study</u>: 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

<u>Clinical trial</u>: 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 single PK study in children will be completed before the initiation of 2 Phase 3 clinical trials to evaluate safety in a step-wise approach in adolescents to children as described above.

	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
	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
	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
	\square Initial ogenicity as a marker of safety \square Other (provide explanation)
	PREA-required efficacy and safety randomized clinical trial
	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
	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?
- $\overline{\boxtimes}$ 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 <u>each</u> PMR/PMC in the Action Package.

NDA/BLA #	BLA 761032	
Product Name:	Siliq (brodalumab) injection, 210 mg/ 1.5 mL	
PMR/ Description:		
	Open label, single arm study with brodalumab to determine efficacy in children (6 to <12) with severe plaque psoriasis	e safety and
PMR Schedule Milestones	: Final Protocol Submission:	02/2024
	Study/Trial Completion:	01/2029
	Final Report Submission:	06/2029
	Other:	MM/DD/YYYY

- 1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.
 - Unmet need
 Life-threatening condition
 Long-term data needed
 Only feasible to conduct post-approval
 Prior clinical experience indicates safety
 Small subpopulation affected
 Theoretical concern
 Other

Moderate to severe psoriasis is uncommon in the pediatric population, representing fewer than 10% of all cases of psoriasis affecting the pediatric population. A waiver is requested for children < 6 years of age based on the fact that necessary studies are impossible or highly impracticable because of the small number of children with the disease. A deferral was requested for children and adolescent's 6 to < 18 years of age. Trials in adults are ready for approval.

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."

Three studies are proposed to assess the safety and efficacy and dosing of brodalumab in the relevant pediatric population.

- Study 1- 20130249- Phase 1 PK study in children and adolescents.
- Study 2- Phase 3 study in adolescents 12 years to < 18 years.
- Study 3- Phase 3 study in children $^{(b)}_{(4)}$ years to < 12 years.

The designs of the studies are to evaluate PK in children and adolescents to extrapolate efficacy from the adult population. The Phase 3 designs are to provide step-wise approach to safety in treating the pediatric population.

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

<u>Clinical trial</u>: 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 single PK study in children will be completed before the initiation of 2 Phase 3 clinical trials to evaluate safety in a step-wise approach in adolescents to children as described above.

Require	ed
Obs	servational pharmacoepidemiologic study
🗌 Reg	gistry studies
Primar	y safety study or clinical trial
\square Pha	rmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
	anough Q-1 chinical that
	inclinical study (laboratory resistance, receptor affinity, quality study related to safety)
Pharma	acokinetic studies or clinical trials
Dru	g interaction or bioavailability studies or clinical trials
Dos	sing trials
<u>Continuc</u>	ation of Question 4
	litional data or analysis required for a previously submitted or expected study/clinical trial
(pr	ovide explanation)
Met	ta-analysis or pooled analysis of previous studies/clinical trials
	nunogenicity as a marker of safety
	er (provide explanation)
<u> </u>	
Agreed	upon:
🗌 Qua	ality study without a safety endpoint (e.g., manufacturing, stability)
Pha	rmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background
rate	es of adverse events)
Clir	nical trials primarily designed to further define efficacy (e.g., in another condition, different disease
sev	rerity, or subgroup) that are NOT required under Subpart H/E
	se-response study or clinical trial performed for effectiveness
Nor	iclinical study, not safety-related (specify)
Oth	er
Is the P	PMR/PMC clear, feasible, and appropriate?
	$r_{\rm eff}$ the study/alinical trial most evidence for DMDs $r_{\rm eff}$ DMCs $r_{\rm eff}$
⊠ Do	bes the study/chinical trial meet criteria for PMIKS or PMICs?

- 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 <u>each</u> PMR/PMC in the Action Package.

NDA/BLA # Product Name:	BLA 761032 Siliq (brodalumab) injection, 210 mg/ 1.5 mL	
MR Description: Conduct a retrospective cohort study using administentify pregnancy outcomes in a cohort of women psoriasis exposed to brodalumab versus a non-bromedication exposure cohort. The outcomes will in malformations, spontaneous abortions, stillbirths, age births. This study may use multiple data source sufficient sample size as women with psoriasis ar systemic treatments while trying to conceive and pregnancy.		tabases to agnosis of ystemic or congenital for gestational to obtain a l to avoid course of
PMR Schedule Milestones	: Final Protocol Submission:	12/2017
	Study/Trial Completion:	12/2022
	Final Report Submission:	06/2023
	Other:	N/A

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

Adult trials are completed and ready for approval. Pregnant women were excluded from these previous trials and some data in this population is needed.

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 plaque psoriasis occurs in women of child bearing age. Therefore we expect there will be some exposure of pregnant women. Data on use of brodalumab in pregnant women is 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

<u>Clinical trial</u>: 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

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Required
Kequired 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
Noneminear study, not safety-related (specify)
Other
Is the PMR/PMC clear, feasible, and appropriate?
\square Does the study/clinical trial meet criteria for PMRs or PMCs?
$ \wedge $ Are the objectives clear from the description of the PMK/PMU?

 \boxtimes 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

5.

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 <u>each</u> PMR/PMC in the Action Package.

NDA/BLA # Product Name:	BLA 761032 Siliq (brodalumab) injection, 210 mg/ 1.5 mL	
PMR Description:	Conduct a prospective, registry-based observation that compares the maternal, fetal, and infant outco diagnosis of psoriasis exposed to brodalumab dur unexposed control population. The registry will co minor congenital malformations, spontaneous ab terminations, small for gestational age births, and pregnancy outcomes. These outcomes will be asse Infant outcomes, including effects on postnatal g be assessed through at least the first year of life.	nal exposure cohort study omes of women with the ring pregnancy to an letect and record major and ortions, stillbirths, elective d any other adverse sessed throughout pregnancy. rowth and development, will
PMR Schedule Milestones:	Final Protocol Submission:	12/2017
	Study/Trial Completion:	06/2030
	Final Report Submission:	06/2031
	Other:	N/A

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

Adult trials completed and ready for approval. Pregnant women were excluded from these trials and data in this population is needed.

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. Data on use of brodalumab in pregnant women is 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

<u>Study</u>: 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

<u>Clinical trial</u>: 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 with psoriasis and neonates.

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Rea	uired
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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
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	nt question	about th	e public	health	risks	of an	approved	drug
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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 <u>each</u> PMR/PMC in the Action Package.

NDA/BLA # Product Name:	761032 Siliq (brodalumab) injection, 210 mg/ 1.5 mL
PMR/PMC Description:	Conduct a prospective, observational study to assess the long-term safety of Siliq (brodalumab) 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 malignancy. Secondary outcomes include, but are not limited to, opportunistic infections (e.g., tuberculosis [TB], opportunistic mycoses) and neutropenia. Describe and justify the choice of appropriate comparator population(s) and estimated background rate(s) relative to brodalumab-exposed patients; clearly define the primary comparator population for the primary objective. Design the study around a testable hypothesis to assess, with sufficient sample size and power, a clinically meaningful increase in malignancy risk above the comparator background rate(s), with a pre-specified statistical analysis method. Specify concise case definitions and validation algorithms for both primary and secondary outcomes. For the brodalumab-exposed and comparator(s) cohorts, clearly define the study drug initiation period, including any exclusion and inclusion criteria. Enroll patients over an initial 4 year period and follow for a minimum of 8 years from the time of enrollment.

PMR/PMC Schedule Milestones:	Draft Protocol Submission	08/2017
	Final Protocol Submission:	03/2018
	Study/Trial Completion:	11/2030
	Final Report Submission:	11/2031
	Other:	

- 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
 ⊠ Only feasible to conduct post-approval
 □ Prior clinical experience indicates safety
 □ Small subpopulation affected
 ⊠ Theoretical concern
 □ Other

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 specific opportunistic infections and neutropenia.

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 theoretical concern that this new biologic product may increase the risk of malignancies, opportunistic infections, and neutropenia due to its immunosuppressive effect.

DEPI-I has determined that an analysis of spontaneous postmarketing adverse events reported under subsection 505(k)(1) of the FDCA and the new pharmacovigilance system established under section 505(k)(3) will not be sufficient to identify the unexpected serious risks of malignancy, opportunistic infections and neutropenia related to the use of brodalumab. DEPI-I therefore requests a required postmarketing safety study (PMR) under section 901 of FDAAA 2007 Title IX to identify an unexpected serious risk when available data indicates the potential for a serious risk related to the use of brodalumab.

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

<u>Study</u>: 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

<u>Clinical trial</u>: 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, observational study to assess the long-term safety of Siliq (brodalumab) 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.

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 <u>each</u> type of CMC PMR/PMC in the Action Package. See #4 for a list of CMC PMR/PMC types

BLA #	761032
Product Name:	Siliq (brodalumab) injection, 210 mg/ 1.5 mL
PMC #1 Description:	Submit final study report for LC/UV/MS analysis using appropriate control samples to confirm the capability of this method to detect volatile compounds in the presence of brodalumab drug product

PMC Schedule Milestones:	Final Report Submission:	03/2017
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- ADD MORE AS NEEDED USING THE SAME TABULAR FORMAT FOR EACH PMC.
- INCLUDE DESCRIPTIONS AND MILESTONES IN THE TABLE ABOVE FOR ALL CMC/OBP NON-REPORTABLE PMCS FOR WHICH THE FOLLOWING ANSWERS WILL BE IDENTICAL.USE A SEPARATE TEMPLATE FOR EACH PMR/PMC FOR WHICH THE ANSWERS TO THE FOLLOWING QUESTIONS DIFFER.
- *DO NOT USE THIS FORM* IF ANY STUDIES WILL BE REQUIRED UNDER FDAAA OR WILL BE PUBLICALY REPORTABLE
- 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 extractables and leachables studies and the clinical studies indicate that the presence of leachates from the brodalumab commercial container closure systems do not appear to be a significant safety or product quality issue. However, the extent of container closure component leaching is not clear, because the capability of the LC/UV/MS method to detect volatile compounds was not demonstrated. Data from an analysis of the overall capability of the LC/UV/MS method to detect volatile leachates that can be introduced into the drug product under long term storage conditions.

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

The 24 month, real-time 2.25 mL syringe leachable study includes the identification and quantification of potential volatile and semi-volatile compounds using an LC/UV/MS method. Data to demonstrate the capability of the LC/UV/MS method to detect volatile compounds are currently not available. The verification of the capability of LC/UV/MS method to detect volatile compounds would provide additional assurance of a low risk to patients from any volatile leachates potentially present in the drug product following long term storage.

3. 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
\square	Other

Describe the agreed-upon study:

Perform LC/UV/MS analysis using appropriate volatile compound control samples and provide data from this analysis to confirm the capability of the LC/UV/MS method used in the drug product leachables study to detect volatile compounds.

- 4. To be completed by ONDQA/OBP Manager:
 - \boxtimes Does the study meet criteria for PMCs?
 - \boxtimes Are the objectives clear from the description of the PMC?
 - Has the applicant adequately justified the choice of schedule milestone dates?
 - Has the applicant had sufficient time to review the PMCs, ask questions, determine feasibility, and contribute to the development process?

PMR/PMC Development Coordinator:

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

(signature line for BLAs only)

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

/s/

STROTHER D DIXON 02/14/2017

TATIANA OUSSOVA 02/14/2017

HUMAN FACTORS, LABEL, LABELING, AND PACKAGING REVIEW AMENDMENT

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:	February 13, 2017
Requesting Office or Division:	Division of Dermatology and Dental Products (DDDP)
Application Type and Number:	BLA 761032
Product Name and Strength:	Siliq (brodalumab) Injection 210 mg/1.5 mL Prefilled Syringe (PFS)
Product Type:	Single Ingredient, Combination Product
Rx or OTC:	Rx
Applicant/Sponsor Name:	Valeant Pharmaceuticals Luxembourg S.a.r.l.
Submission Date:	November 16, 2015
OSE RCM #:	2016-2611 and 2015-2612
DMEPA Primary Reviewer:	Carlos M Mena-Grillasca, RPh
OMEPRM Acting Deputy Director:	Lubna Merchant, MS, PharmD

REASON FOR AMENDMENT:

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].

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:	October 4, 2016
Requesting Office or Division:	Division of Dermatology and Dental Products (DDDP)
Application Type and Number:	BLA 761032
Product Name and Strength:	Siliq (brodalumab) Injection 210 mg/1.5 mL Prefilled Syringe (PFS)
Product Type:	Single Ingredient, Combination Product
Rx or OTC:	Rx
Applicant/Sponsor Name:	Valeant Pharmaceuticals Luxembourg S.a.r.l.
Submission Date:	November 16, 2015
OSE RCM #:	2016-2611 and 2015-2612
DMEPA Primary Reviewer:	Carlos M Mena-Grillasca, RPh
DMEPA Team Leader:	Mishale Mistry, PharmD, MPH
DMEPA Associate Director for Human Factors:	QuynhNhu Nguyen, MS

1 REASON FOR REVIEW

This review evaluates the applicant's Human Factors (HF) validation study report, the proposed container label, carton labeling, Prescribing Information (PI), and Instructions for Use (IFU) for Siliq (brodalumab) injection (BLA 761032) in responding to the consult request from the Division of Dermatology and Dental Products (DDDP). This is a 351k submission containing a PFS and the drug product Siliq, intended to treat moderate to severe plaque psoriasis.

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.

Table 1. Materials Considered for this Label and Labeling Review			
Material Reviewed	Appendix Section (for Methods and Results)		
Product Information/Prescribing Information	A		
Previous DMEPA Reviews	В		
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

The Applicant proposes a standard, single dose, pre-filled syringe (PFS) with a flange extender for Siliq (2.25 mL glass (Type 1) syringe with a staked in place stainless needle). DMEPA did not request that the Applicant conduct a HF validation study for the proposed PFS nor reviewed the HF study protocol. We noted an issue regarding the representativeness of the study participants to the intended users in that all of the participants had high school education or higher, which is not representative of the US literacy level.

Nevertheless, our review of the results showed that 77 of the 80 participants performed all steps successfully. A total of three use errors were committed on essential steps by three moderator-trained participants (2 patients and 1 caregiver):

- One moderator-trained patient and one moderator-trained caregiver participant lost the medication prior to administration as a result of the plunger rod pushing down on the tabletop during cap removal. This action resulted in a stream of medication onto the table and surrounding area.
- One moderator-trained, injection-naïve participant failed to push the plunger upon needle insertion. The participant indicated that he/she expected that the syringe would inject the medication on its own. Additionally, the participant stated the he/she did not know that they had access to the IFU for the simulated injection and stated that they would have used the instructions

at home. The participant self-detected the use error during the root cause interview and then went on to demonstrate a successful injection.

Our evaluation of these errors indicated that they are associated with first time use of injectable products administered via PFS and may not recur, as shown in the study that the users would detect and correct the error immediately. We further evaluated the risks associated with the use of the product and did not identify any new or unique risks compared to currently marketed prefilled syringes for this patient population and for this indication. As such, we do not have any recommendations to further mitigate the errors.

In addition, we noted multiple use-errors on non-essential tasks (e.g. checking expiration date, inspection the drug appearance, inspection for damage, clean injection site, washing hands). See Appendix C for more details. We do not have any recommendations to address the use errors at this time.

Regarding the proposed label and labeling, we note the following deficiencies:

- The presentation of the strength statement can be improved to increase readability. As currently presented there is no space between the numbers and the unit of measure (i.e. proposed 210mg/1.5mL vs. recommended 210 mg/1.5 mL).
- The ^{(b) (4)} on the container label interfers with the legibility of information.
- The strength statement, as presented within the orange circle on the carton labeling, does not include the total volume (i.e. proposed 210 mg vs. recommended 210 mg/1.5 mL) in accordance with USP General Chapter <1>.
- The carton labeling include two statements related to dosing: (b) (4) (b) (4)

^{(b) (4)}. Including two different statements related to dosing

may be confusing for end users.

4 CONCLUSION & RECOMMENDATIONS

We find the HF validation study results acceptable. We identified areas for improvement with regards to the visual display of the strength on the container labels and carton labeling of the proposed product. Additionally, we identified other aspects of the labels and labeling that should be revised to improve readability of important information and promote the safe use of the product. We provide letter-ready recommendations for Valeant Pharmaceuticals Luxembourg S.a.r.l. in Section 4.1 below, to be implemented prior to approval of BLA 761032.

4.1 RECOMMENDATIONS FOR VALEANT PHARMACEUTICALS LUXEMOURG S.a.r.l.

- A. General Comments (All container labels and carton labeling)
 - 1. Revise the strength statement to include a space between the number and the unit of measure (i.e. 210 mg/1.5 mL) to improve legibility.
- B. Container Label
 - 1. Delete the ^{(b) (4)} to prevent clutter and improve legibility on these small labels.
- C. Carton Labeling (sample and trade)
 - 1. Revise the strength statement presented within the orange circle to include the total volume (i.e. 210 mg/1.5 mL) in accordance with USP Chapter <1>.
 - 2. On the principal display panels (top and side panels with the orange box), re-locate the statement within the orange box that reads "See package insert for ^{(b) (4)} and instructions for

use" to the top of the box and revise to read "See package insert for dosing information and Instructions for Use".

- 3. On the principal display panel (top panel), delete the statement " (b) (4)
 " as users are referred to the package insert and instructions for use in other sections of the carton labeling.
- D. Carton Labeling (sample)
 - 1. On the principal display panels (top and side panels with the orange box), relocate the route of administration statement to appear below the strength statement (where the sample statement is currently presented).
 - 2. In order to implement recommendation D.1., relocate the sample statement to the location where the route of administration statement is currently presented.
- E. Carton Labeling (trade)
 - 1. On the principal display panel (side panel with the orange box), relocate the route of administration statement to appear below the strength statement.

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Siliq that Valeant Pharmaceuticals Luxembourg S.a.r.l. submitted on August 12, 2016.

Table 2. Relevant Product Information for Siliq				
Initial Approval Date	N/A			
Active Ingredient	Brodalumab			
Indication	Treatment of moderate to severe plaque psoriasis in adult patients who are candidates for systemic therapy or phototherapy			
Route of Administration	Subcutaneous			
Dosage Form	Injection			
Strength	210 mg/1.5 mL			
Dose and Frequency	210 mg by subcutaneous injection at Weeks 0, 1, and 2 followed by 210 mg every 2 weeks			
How Supplied	Sample: Carton of 1- 210 mg/1.5 mL PFS Trade: Carton of 2- 210 mg/1.5 mL PFS			
Storage	Refrigerated at 2°C to 8°C (36°F to 46°F)			
Container Closure	2.25 mL glass (Type 1) syringe with a staked in place stainless steel needle			

APPENDIX B. PREVIOUS DMEPA REVIEWS

B.1 Methods

On Septemebr 15, 2016 we searched the L:drive using the term, Siliq and brodalumab, to identify reviews previously performed by DMEPA.

B.2 Results

Our search did not identified any previous relevant review.

APPENDIX C. PREFILLED SYRINGE HUMAN FACTORS STUDY RESULTS

Objectives

The first objective of this study was to validate, through objective and subjective evidence, that participants representative of the intended user population can safely demonstrate proficiency with the following essential steps:

Remove the prefilled syringe from packaging

Remove needle shield by pulling straight off

Place injection needle on recommended injection site surface and pierce the skin (simulation with skin pad)

Depress the syringe plunger rod to empty the entire drug product

Remove device from injection site without needle-stick injury

Dispose of device without needle-stick injury

The second objective of this study was to assess performance of these tasks under learning decay conditions.

Intended User Population, Intended Use and Use Environments

The Siliq PFS intended user population includes HCPs, caregivers, and patients. The Siliq PFS is a singleuse, disposable device intended to administer a fixed dose of brodalumab drug product into the subcutaneous tissue (abdomen, thigh, or outer area of upper arm) of patients for the treatment of Plaque Psoriasis and Psoriatic Arthritis. It is intended for use by patients and caregivers in a non-healthcare environment or by HCPs in a clinical setting.

Device Configuration

Siliq PFS will be commercially available in 1.5 mL fill volume for a 210 mg dose.

Packaging Configurations

This study evaluated the two-pack packaging configuration for Siliq PFS. The larger package (two-pack) was used for this study because it was considered the most challenging usage scenario; specifically, users had to first determine the correct number of syringes to use for the simulated drug administration.

Participant Demographics

The study sample consisted of 80 participants from three user groups: 1) Patients (n=32), 2) Caregivers (n=32) and 3) HCPs (n=16). See Table 10 for participant demographic information.
Table 10: Demographics - 1.5 mL Fill PFS with Standard IFU

Demographics	Recruited Participants			
	Patients (n=32) - 49 years old (range: 21-70)			
A	Caregivers (n=32) - 44 years old	(range: 24-65)		
Average Age	HCP (n=16) - 48 years old (ran	ige: 32-63)		
	Total (n=80) - 47 years old (ra	nge: 21-70)		
Gender	56 Female, 24 Male	2		
	Patients - 19 naïve, 13 expe	erienced		
Injection Experience (Patients and Caregivers Only)	Caregivers - 14 naïve, 18 exp	perienced		
	Total - 33 naïve, 31 experienced			
Average HCP Experience (HCPs Only)	19 years as HCP (range: 4-40)			
	Level	Frequency		
	Moderate	7		
Hand Dysfunction (Patients Only)	Minor	2		
	None	23		
	Level	Frequency		
	High School	4		
	Some College	21		
Education	Associates	10		
	Bachelors	32		
	Graduate Degree	13		

Learning Decay (Loss of Information Retention) Evaluation

To evaluate the effects of learning decay, moderatortrained participants were provided a 60-minute break between the training and testing portions of the study.

Test Conditions

Moderator-trained: Approximately half of the patient participants and approximately half of the caregiver participants were trained on how to use the PFS by the moderator following a training walk-through script covering key points from the IFU. After training, participants were given a 60-minute break, and then returned to the study room to prepare and administer a complete dose (simulated) using a Siliq PFS with Flange Extender Two-Pack Box.

Self-trained: Approximately half of patient participants and approximately half of the caregiver participants were self-trained using the assigned IFU. Participants prepared and administered a complete dose (simulated) using a Siliq PFS with Flange Extender Two-Pack Box

Results

Key Results

According to the Siliq PFS Summative Study Protocol, essential steps were defined as the tasks necessary for successful use of the device for its intended purpose. For the Siliq PFS system, this includes the tasks necessary to enable the patient to receive a complete dose.

A total of 77 out of 80 participants (96%) that used the standard IFU with the 1.5 mL fill PFS successfully completed the tasks necessary to administer a complete dose.

Table 11 below lists each essential step and the corresponding performance rate by distinct user group (i.e., patient, caregiver, and HCP) and training condition (i.e., moderator-trained vs. self-trained). Performance rate is defined as the percentage of participants that completed a given step without committing a use error during the study.

Performance was nearly the same with the 1.5 mL fill PFS with standard IFU for training conditions and user groups with respect to essential steps; a total of 3 out of 32 moderator trained participants committed 3 essential step use errors (2 by patients and 1 by a caregiver), while 0 out of 48 self-trained participants committed 0 essential step use errors.

Essential Stens	Moderator-Trained (n=32)		Self-Trained (n=48)		
Lasennal Steps	Patient	Caregiver	Patient	Caregiver	HCP
	(n=16)	(n=16)	(n=16)	(n=16)	(n=16)
Remove device from packaging	100%	100 %	100 %	100 %	100 %
	16 / 16	16 / 16	16 / 16	16 / 16	16 / 16
Remove needle cover	94%	94 %	100 %	100 %	100 %
	15 / 16	15 / 16	16 / 16	16 / 16	16 / 16
Place injection needle on injection site surface and pierce the skin	100 %	100 %	100 %	100 %	100 %
	16 / 16	16 / 16	16 / 16	16 / 16	16 / 16
Depress the syringe plunger rod to	94 %	100 %	100 %	100 %	100 %
empty the entire drug product	15 / 16	16 / 16	16 / 16	16 / 16	16 / 16
Remove device from injection site without needle-stick injury	100 %	100 %	100 %	100 %	100 %
	16 / 16	16 / 16	16 / 16	16 / 16	16 / 16
Dispose of device without needle stick injury	100 %	100 %	100 %	100 %	100 %
	16 / 16	16 / 16	16 / 16	16 / 16	16 / 16

|--|

Table 13 shows there were a total of 3 essential step use errors committed by 3 participants.

Table 13: Number of Essential Step Use Errors

Essential Stens	Moderator-Trained (n=32)		Self-Trained (n=48)		
	Patient (n=16)	Caregiver (n=16)	Patient (n=16)	Caregiver (n=16)	HCP (n=16)
Remove device from packaging	0	0	0	0	0
Remove needle cover	1	1	0	0	0
Place injection needle on injection site surface and pierce the skin	0	0	0	0	0
Depress the syringe plunger rod to empty the entire drug product	1	0	0	0	0
Remove device from injection site without needle-stick injury	0	0	0	0	0
Dispose of device without needle stick injury	0	0	0	0	0
Total	2	1	0	0	0

According to the Siliq PFS Summative Study Protocol, safety critical use errors were defined as hazards/failures identified in the uRA with a severity of 5 or higher.

A total of 69 use errors with a severity of 5 or higher were committed by 49 out of the 80 participants. Note that 34 of these 69 use errors (49%) were failures to check the expiry date.

Table 12 below lists each IFU step associated with a use error with a severity of 5 or higher and the corresponding performance rate by distinct user group and training condition. Performance rate is defined as the percentage of participants that completed a given step without committing a use error during the study.

Performance was nearly the same for training conditions and user groups with respect to these use errors, for the exception of HCPs, who on average committed slightly fewer of these use errors than patients and caregivers; a total of 21 out 32 moderator-trained participants (10 patients, 11 caregivers) committed 27 of these 69 use errors, while 28 out of 48 self-trained participants (11 patients, 10 caregivers, 7 HCPs) committed the remaining 42 use errors.

Table 12: Performance Rate for IFU Steps Associated with Use Errors with a Severity of 5 or Higher for 1.5 mL Fill PFS with Standard IFU

IFU Steps Associated	Moderator-Trained (n=32)		Self-Trained (n=48)		
Severity of 5 or Higher	Patient	Caregiver	Patient	Caregiver	HCP
	(n=16)	(n=16)	(n=16)	(n=16)	(n=16)
Inspect drug appearance	100%	81 %	94%	100 %	88 %
	16 / 16	13 / 16	15 / 16	16 / 16	14 / 16
Inspect for damage	88 %	88 %	94 %	94%	94 %
	14 / 16	14 / 16	15 / 16	15 / 16	15 / 16
Check expiration date	63 %	56%	63 %	44%	63 %
	10 / 16	9 / 16	10 / 16	7 / 16	10 / 16
Wash hands	69 %	75 %	88 %	100 %	94 %
	11 / 16	12 / 16	14 / 16	16 / 16	15 / 16
Clean site with alcohol wipe	94%	88 %	69 %	88%	100 %
	15 / 16	14 / 16	11 / 16	14 / 16	16 / 16

Table 14 shows there were a total of 69 use errors committed by 49 participants.

Table 14: Number of IFU Step Use Errors with a Severity of 5 or Higher for 1.5 mL Fill PFS with Standard IFU

IFU Steps Associated	Moderator-Trained		Self-Trained		
with Use Errors with a Severity of 5 or Higher	Patient (n=16)	Caregiver (n=16)	Patient (n=16)	Caregiver (n=16)	HCP (n=16)
Inspect drug appearance	0	3	1	0	2
Inspect for damage	2	2	1	1	1
Check expiration date	6	7	6	9	6
Wash hands	5	4	2	0	1
Clean site with alcohol wipe	1	2	5	2	0
Total	14	18	15	12	10

Summary Conclusions 1.5 mL Fill PFS with Standard IFU

- A total of 77 out of 80 participants (96%) that used the standard IFU with the 1.5 mL fill PFS successfully completed the tasks necessary to administer a complete dose.
- Performance was nearly the same for training conditions and user groups with respect to
 essential steps.
- Performance was nearly the same for training conditions and user groups with respect to
 use errors with a severity of 5 or higher, for the exception of HCPs who on average
 committed slightly fewer of these use errors than patients and caregivers.

APPENDIX D. ISMP NEWSLETTERS

N/A

APPENDIX E. FDA ADVERSE EVENT REPORTING SYSTEM (FAERS) N/A

APPENDIX F. OTHER

APPENDIX G. LABELS AND LABELING

G.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,¹ along with postmarket medication error data, we reviewed the following Siliq labels and labeling submitted by Valeant Luxembourg on June 17, 2016.

(b) (4)

- Container label
- Carton labeling
- Prescribing Information (not pictured)
- Instructions for Use (not pictured)

G.2 Label and Labeling Images (not to scale)



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/s/

CARLOS M MENA-GRILLASCA 02/13/2017

LUBNA A MERCHANT 02/13/2017

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

OSE RCM #	2015-2628
Reviewer Name(s)	Erin M. South, Pharm.D. Ana Tavakoli, M.A.
Team Leader (Acting)	Donella Fitzgerald, Pharm.D.
Deputy Division Director (Acting)	Jamie Wilkins Parker, Pharm.D.
Review Completion Date	January 9, 2017
Subject	Review of REMS Proposal
Established Name	Brodalumab
Applicant	Valeant Pharmaceuticals
Application Number	761032
Therapeutic Class	Interleukin (IL)-17A antagonist
Formulation(s)	210 mg/1.5 mL single-use pre-filled syringe (140 mg/mL)
Dosing Regimen	210 mg subcutaneous injection at Weeks 0, 1, and 2, followed by 210 mg every 2 weeks
Proposed Indication(s)	Treatment of adult patients with moderate-to-severe plaque psoriasis who are candidates for systemic therapy or phototherapy

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Table of Contents

1 Introduction

This review by the Division of Risk Management (DRISK) evaluates the proposed risk evaluation and mitigation strategy (REMS) for the new molecular entity (NME) Siliq (brodalumab) submitted by the Applicant on November 16, 2015, and amended on February 4, October 18, December 16, and December 22, 2016. An original Biologics Licensing Application (BLA 761032) was submitted by AstraZeneca on November 16, 2015, for the treatment of adult patients with moderate-to-severe plaque psoriasis who are candidates for systemic therapy or phototherapy. The proposed REMS consists of elements to assure safe use (ETASU) and a timetable for submission of assessments. This application is under review in the Division of Dermatology and Dental Products (DDDP). Ownership of the application was transferred from AstraZeneca to Valeant Pharmaceuticals North America, LLC (Valeant) on April 1, 2016.

DRISK and DDDP agree that a REMS is needed to ensure the benefits of Siliq outweigh its risks. The REMS requires elements to assure safe use (ETASU), including health care providers who prescribe the drug are specially certified, pharmacies that dispense the drug are specially certified, and the drug be dispensed to patients with evidence or other documentation of safe-use conditions.

The Applicant was informed of our determination regarding the need for an ETASU REMS in a meeting between the Agency and the Applicant on August 22, 2016. Valeant submitted a REMS amendment to the BLA on October 18, 2016. On December 13, 2016, the Agency provided initial comments, based on review of the October 18, 2016 submission, and advised the Applicant that the REMS document was still under review. The Applicant subsequently submitted REMS amendments on December 16 and December 22, 2016, which are the subjects of this review.

2 Background

2.1 PRODUCT INFORMATION

Siliq, a new molecular entity, is a human IgG2 monoclonal antibody (mAb) that binds to the human interleukin-17 receptor A (IL-17RA), preventing IL-17 from activating the receptor, and, therefore, blocks the biological activities of IL-17A, IL-17C, IL-17F, IL-17A/F heterodimer and IL-25. The Applicant-proposed formulation and dosing regimen for Siliq is a 210 mg/1.5 mL single-use prefilled syringe (140 mg/mL), intended for chronic treatment as a 210 mg subcutaneous (SC) injection at Weeks 0, 1, and 2, followed by 210 mg every 2 weeks, and is likely to be administered by patients or caregivers in the home setting. Population-based pharmacokinetic simulations estimate that serum Siliq concentrations for 95% of subjects would drop below the limit of detection approximately 32 days and 63 days after discontinuing treatment with Siliq 140 mg Q2W and 210 mg Q2W, respectively.

The proposed mechanism of action of Siliq is similar to that of another anti-psoriasis mAb, ixekizumab, which, however, binds to IL-17 itself. BLA 125521 for ixekizumab (Taltz) was approved March 22, 2016, without a REMS, for the treatment of adults with moderate-to-severe plaque psoriasis who are candidates for systemic therapy or phototherapy.

On July 4, 2016, the Japanese Authority approved brodalumab for marketing in Japan. Additionally, the Applicant has submitted a Marketing Authorization Application to the European Medicines Agency (EMA) for brodalumab for the treatment of moderate-to-severe plaque psoriasis in adults.

2.2 **REGULATORY HISTORY**

The following is a summary of the regulatory history for the proposed REMS relevant to this review (further detailed regulatory history is available in review RCM 2015-2628, dated December 12, 2016):

<u>November 16, 2015</u>: AstraZeneca submitted BLA 761032, for the treatment of adult patients with moderate-to-severe plaque psoriasis who are candidates for systemic therapy or phototherapy. The submission included a REMS, consisting of a Medication Guide, communication plan, and timetable for submission of assessments; the goals were to inform healthcare providers about the potential risk of SIB in patients with psoriasis and the importance of proper patient selection, and to educate patients to recognize the signs and symptoms of changes in their mental health, and to seek intervention should such signs emerge.

<u>April 1, 2016</u>: Ownership of BLA 761032 was transferred from AstraZeneca to Valeant Pharmaceuticals, North America LLC.

<u>August 9, 2016</u>: A second meeting of the ROC was held. The ROC recommended that a REMS with ETASU was necessary for the approval of brodalumab, in order to ensure the benefits of brodalumab outweigh its risks.

October 18, 2016: Valeant submitted an amendment to their REMS proposal.

<u>December 13, 2016</u>: The Agency provided comments to the Applicant and the Agency's redlined REMS materials, based on review of the Applicant's REMS amendment submitted on October 18, 2016.

<u>December 16, 2016</u>: Valeant submitted a REMS amendment to BLA 761032 in response to the Agency's December 13, 2016 comments; the submission was incomplete as it did not include the necessary REMS appended materials and REMS website screenshots.

<u>December 22, 2016</u>: Valeant submitted a REMS amendment to BLA 761032; the submission, despite including the REMS materials omitted from the Applicant's December 16, 2016

submission, was incomplete because it did not include a REMS document and REMS supporting document.

3 Risk Management Activities Proposed by the Applicant

3.1 REVIEW OF THE APPLICANT'S PROPOSED REMS

The Applicant submitted REMS amendments to BLA 761032 on December 16, and December 22, 2016, in response to the Agency's December 13, 2016 comments. This review evaluates and provides comments on the Applicant's December 16, and December 22, 2016 REMS amendments, which together would have comprised a complete submission if their respective elements were combined and submitted as a single REMS amendment. The revised REMS document and materials require additional revisions to be acceptable; a single, complete REMS submission will also be required.

3.2 REMS DOCUMENT

The Applicant's proposed REMS document has been revised to include ETASU; however, additional revisions to the REMS document are required, for it to be acceptable.

REMS Goals

The Applicant's December 16, 2016 submission proposes the following REMS goal:

To mitigate the potential risk of suicidal ideation and behavior by:

- Ensuring that prescribers are educated about the potential risk of suicidal ideation and behavior observed with SILIQ therapy and the need to counsel patients about this risk.
- Ensuring that patients are informed about the potential risk of suicidal ideation and behavior observed with SILIQ therapy and the need to seek medical attention should they experience emergence or worsening of suicidal thoughts and behavior.

Reviewer Comment: In the Applicant's December 16, 2016 submission, the proposed REMS goals have been revised to align with the Agency's December 13, 2016 recommendations. The proposed REMS goals are acceptable.

Medication Guide

The Applicant's December 16, 2016 submission proposes to remove the Medication Guide from the REMS, as requested by the Agency.

Reviewer Comment: A Medication Guide is not required as an element of the REMS; therefore, we find the removal of the Medication Guide from the REMS to be acceptable.

Elements to Assure Safe Use (ETASU)

The Applicant has proposed ETASU to include: prescriber enrollment (A), pharmacy enrollment (B), and documentation of safe-use conditions (D).

Reviewer Comment: The Agency agrees that the REMS program should include the above elements. However, the Applicant's proposed REMS document requires further revision, to be acceptable. Following the Agency's comments and redlined materials sent to the Applicant on December 13, 2016, the Agency is requiring additional minor revisions to the language to improve clarity and more clearly detail the responsibilities of the prescribers, pharmacies, and patients. Refer to the attached redlined REMS document.

REMS Website

The Applicant's proposed REMS website screenshots, as submitted by the Applicant on December 22, 2016, include references to materials that are not included in the REMS (e.g., Medication Guide, Healthcare Provider Fact Sheet).

Reviewer Comment: The REMS website requires significant revisions to be acceptable. The website should accurately reflect the REMS elements and materials, as outlined in the REMS document. Therefore, the proposed REMS website should be revised to remove reference to materials that are not included in the REMS (e.g.,

), and include only the appropriate REMS materials.

There should be only one tab for "Pharmacies." Additionally, the language in the "Indication" and "Limitations of Use" sections should not be included on the REMS home page. The "Hours of Operation" banner should not be included on every page and contact information should be included only where necessary. The language corresponding to, "What is the SILIQ REMS Program" should be revised to the following:

- A REMS is a strategy to manage known or potential serious risks associated with a drug product, and is required by the FDA to ensure the benefits of a drug outweigh its risks.
- The purpose of the SILIQ REMS Program is to mitigate the potential risk of suicidal ideation and behavior (SIB) associated with SILIQ by:
 - Ensuring that prescribers are educated about the potential risk of suicidal ideation and behavior observed with SILIQ therapy and the need to counsel patients about this risk
 - Ensuring that patients are informed about the potential risk of suicidal ideation and behavior observed with SILIQ therapy and the need to seek medical attention should they experience emergence or worsening of suicidal thoughts and behavior.

Additionally, the language on page 7 should be revised to the following:

Patient's Role in the SILIQ REMS Program:

 Only patients who are counseled on the safe use of SILIQ by their prescriber should be prescribed SILIQ. Patients should be counseled on the SILIQ REMS Program by certified prescribers and given the opportunity to discuss any questions or concerns they have with their prescriber. The prescriber should review and provide the SILIQ REMS Program Patient-Prescriber Agreement Form to each patient.

3.3 REMS APPENDED MATERIALS

The appended materials require formatting and content changes. The formatting of titles of forms should be consistent throughout. All titles should be listed on the upper right-hand corner of the form with the SILIQ logo placed on the left-hand side of the page. Refer to comments in Section 6.

SILIQ REMS Program Prescriber Enrollment Form

The Applicant's proposed *SILIQ REMS Program Prescriber Enrollment Form* includes revisions to the prescriber attestations and document formatting.

Reviewer Comment: We disagree with the Applicant's proposed revisions to the attestations on the *SILIQ REMS Program Prescriber Enrollment Form.* This document should be revised to align with the redlined document the Agency provided to the Applicant on December 13, 2016.

SILIQ REMS Program Pharmacy Enrollment Form

The Applicant's proposed *SILIQ REMS Program Pharmacy Enrollment Form* includes revisions to the pharmacy authorized representative attestations and document formatting.

Reviewer Comment: We disagree with the Applicant's proposed revisions to the attestations on the *SILIQ REMS Program Pharmacy Enrollment Form*. This document should be revised to align with the redlined document the Agency provided to the Applicant on December 13, 2016.

SILIQ REMS Program Patient-Prescriber Agreement Form

The Applicant's proposed *SILIQ REMS Program Patient-Prescriber Agreement Form* includes revisions to the document formatting.

Reviewer Comment: Following further consideration by the Agency, we recommend revising the language to better align with the REMS goals, as follows:

- □ I will call the National Suicide Prevention Lifeline at 1-800-273-8255 or my doctor if:
 - I feel new or worsening feelings of withdrawal, depression, anxiety, hopelessness, or other mood changes beginning.

• I am (b) (4) thinking (b) about hurting or killing myself; seeking access to firearms, pills or other means for the purpose of self-harm; or am talking or writing about death and dying.

SILIQ REMS Program Patient Wallet Card

The Applicant's December 22, 2016 proposed REMS amendment includes a proposed *SILIQ Patient Wallet Card*.

Reviewer Comment: Following further consideration by the Agency, we recommend revising the language to better align with the REMS goals, as follows:

- □ I will call the National Suicide Prevention Lifeline at 1-800-273-8255 or my doctor if:
 - I feel new or worsening feelings of withdrawal, depression, anxiety, hopelessness, or other mood changes beginning.
 - I am ^{(b)(4)} thinking ^(b) (4) about hurting or killing myself; seeking access to firearms, pills or other means for the purpose of self-harm; or am talking or writing about death and dying.

4 Discussion

The Applicant's REMS proposals, as submitted on December 16, and December 22, 2016, includes the Agency's required ETASU, but requires significant revisions, to be acceptable. Additionally, the REMS proposal should include a REMS document, REMS appended materials, REMS website, and REMS supporting document, which should include the REMS assessment plan, in order for the proposal to be considered complete.

5 Conclusion & Recommendations

DRISK does not find the Applicant's proposed REMS acceptable because further revisions to the REMS document, REMS appended materials, and REMS supporting document are required. Comments for the Applicant are provided in Section 6.

6 Comments for the Applicant

The following comments and the attached redlined REMS document are based on the Agency's review of the proposed REMS for Siliq submitted under BLA 761032. In order to facilitate further review, we ask that you revise your REMS proposal based on the following comments and attached redlined REMS document and resubmit your complete REMS amendment within 7 calendar days, by COB January 17, 2017.

A. General Comments

Refer to the attached redlined REMS document. We also refer you to the revised REMS materials (appended materials, supporting document and assessment plan) provided by

the Agency on December 13, 2016. Your complete REMS proposal should be submitted as separate documents in the same submission, to include both a Word tracked changes version and a Word clean version of each of these documents, as well as a .pdf version of each of the previously mentioned documents and appended materials.

B. REMS Document

Significant revisions to the REMS document are necessary, to be acceptable. The attached redlined REMS document provides the necessary revisions.

C. REMS Appended Materials

The proposed REMS appended materials require revisions to be acceptable. Specifically, the *SILIQ REMS Program Prescriber Enrollment Form* and *SILIQ REMS Program Pharmacy Enrollment Form* should be revised to align with the redlined documents provided to you by the Agency on December 13, 2016.

Keep the formatting of titles of forms consistent throughout. For example, all titles should be listed on the upper right-hand corner of the form with the SILIQ logo placed on the left-hand side of the page. As a reminder, the <u>www.SILIQREMS.com</u> and the toll-free number (855-511-6135) must represent a direct link to only REMS-related information and must not be promotional in tone.

D. REMS Website

The REMS website requires significant revisions to be acceptable, which should include the following:

- The website should accurately reflect the REMS elements and materials described in the REMS document. Therefore, your proposed REMS website should be revised to remove reference to materials that are not included in the REMS

 and include only the appropriate REMS materials.
- Remove the "^{(b)(4)}" language from the REMS home page
- Revise the "What is the SILIQ REMS Program" language as follows:
 - A REMS is a strategy to manage known or potential serious risks associated with a drug product, and is required by the FDA to ensure the benefits of a drug outweigh its risks.
 - The purpose of the SILIQ REMS Program is to mitigate the potential risk of suicidal ideation and behavior (SIB) associated with SILIQ by:
 - Ensuring that prescribers are educated about the potential risk of suicidal ideation and behavior observed with SILIQ therapy and the need to counsel patients about this risk
 - Ensuring that patients are informed about the potential risk of suicidal ideation and behavior observed with SILIQ therapy and the need to seek medical attention should they experience emergence or worsening of suicidal thoughts and behavior.

- Remove the "^{(b) (4)}" tab, as there should be only one tab for "Pharmacies"
- Remove the "^{(b) (4)}" banner from the bottom of every page; include contact information only where necessary
- Ensure the SILIQ logo placed on the REMS webpages does not link back to the product website

Additionally, we refer you to the REMS@FDA website, which references multiple approved REMS programs with REMS websites, which you may find useful.

7 Appendices

1. REMS document, redlined

7.1 SUBMISSIONS

- AstraZeneca, Risk Evaluation and Mitigation Strategy for Brodalumab, BLA 761032, November 16, 2015 (Seq. 0000)
 - Amendment received February 4, 2016 (Seq. 0009)
- Valeant, Risk Evaluation and Mitigation Strategy for Brodalumab, BLA 761032, October 18, 2016 (Seq. 0057)
 - o Amendment received December 16, 2016 (Seq. 0062)
 - o Amendment received December 22, 2016 (Seq. 0063)

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/s/

DONELLA A FITZGERALD 01/09/2017

JAMIE C WILKINS PARKER 01/09/2017

Internal Consults

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

Please Note: The following review is for DRISK only and should not be used to provide comments to the sponsor. Anahita Tavakoli, Health Communications Analyst, DRISK To: Silvia Wanis, Regulatory Review Officer From: CC: Silvia Wanis, Regulatory Review Officer Matthew Falter, Team Leader Tri Bui Nguyen, SRPM, OSE Donella Fitzgerald, Team Leader, DRISK Anahita Tavakoli, Health Communications Analyst, DRISK Carole Broadnax CDER-OPDP-RPM Michael Wade Date: January 4, 2017 BLA # 761032 Re: SILIQ[™] (brodalumab) Injection, for subcutaneous use Comments on draft Risk Evaluation and Mitigation Strategies (REMS) Materials (Submission date: December 27, 2016)

Materials Reviewed

OPDP has reviewed the following proposed REMS materials for SILIQ:

- Healthcare Provider (HCP) REMS Materials:
 - Patient-Prescriber Agreement Form

- Prescriber Enrollment Form
- Pharmacy Enrollment Form
- Direct-to-Consumer (Patient) REMS Material:
 - SILIQTM Patient Wallet Card

The version of the draft REMS materials used in this review were sent from DRISK, Anahita Tavakoli, DRISK Health Communications Analyst, via email on December 27, 2016. The draft REMS materials are attached to the end of this review memorandum.

OPDP offers the following comments on these draft REMS materials for SILIQ.

General Comment

Please remind Valeant that REMS materials are not appropriate for use in a promotional manner.

OPDP notes the link <u>www.SILIQREMS.com</u> and toll free numbers such as 1-855-511-6135. OPDP recommends that these items represent a direct link to only REMS related information and not be promotional in tone.

REMS Materials

OPDP does not object to including the following materials in the REMS program (please see Specific Comments below):

- Patient-Prescriber Agreement Form
- Prescriber Enrollment Form
- Pharmacy Enrollment Form
- o Patient Wallet Card

Specific Comments

OPDP considers the following statements promotional in tone and recommends revising or deleting them from the REMS piece:

- Patient Wallet Card
 - o Indications/Use
 - "SILIQ is indicated for the treatment of moderate to severe plaque psoriasis in adult patients who are candidates for systemic therapy or phototherapy."

 This statement inadequately presents the indication for Siliq by omitting important material information pertinent to the REMS risks. Specifically, this statement does not include information regarding the drug's place in therapy due to the risk of suicidal ideation and behavior. Therefore, we recommend that the claim be revised to include the full approved indication: "SILIQ™ is indicated for the treatment of moderate to severe plaque psoriasis in adult patients who are candidates for systemic therapy or phototherapy and have failed to respond or have lost response to other systemic therapies."

(b) (4)

o Risk

- WARNING:
 - This claim omits REMS specific risk. We recommend that the claim be revised to include the specific REMS risk: "Suicidal thoughts and behavior, including completed suicides, have occurred in patients treated with SILIQ."

o Benefit

- O (b) (4)
 - This claim focuses on promoting the benefits of the treatment rather than on educating about the serious risks of treatment. In addition, this claim is redundant, since information about efficacy of the product is included in the indication statement. We recommend removing this claim from the Patient Wallet Card.

However, if this claim is not removed, we recommend revising the claim to include material information in order to accurately convey the patient population in which efficacy was established. For example, "Taking SILIQ has proven effective for the treatment of moderate to severe plaque psoriasis in adult patients who are candidates for systemic therapy or phototherapy." (emphasis added)

Patient-Prescriber Agreement Form

o Risk	
0	(b) (4)
	• This claim omits REMS specific risk. We recommend that the claim be revised to include the specific REMS risk: "Suicidal thoughts and behavior, <u>including</u> <u>completed suicides, have occurred</u> in patients treated with SILIQ."
Prescriber En	ollment Form
o Risk	



 This claim omits REMS specific risk. We recommend that the claim be revised to include the specific REMS risk: "Suicidal thoughts and behavior, <u>including</u> <u>completed suicides, have occurred</u> in patients treated with SILIQ."

We have no additional comments on these proposed REMS materials at this time.

Thank you for your consult.

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/s/

SILVIA WANIS 01/04/2017



Department of Health and Human Services

Food and Drug Administration

Center for Drug Evaluation and Research | Office of Surveillance and Epidemiology (OSE)

Date:	December 14, 2016
Reviewer:	Andrew D. Mosholder, MD MPH
	Division of Epidemiology 1
Team Leader:	Sukhminder K. Sandhu, PhD MPH MS
	Division of Epidemiology 1
Deputy Director (acting):	Simone Pinheiro, ScD MSc
	Division of Epidemiology 1
Subject:	Active Risk and Identification Analysis (ARIA) Sufficiency Memo
Drug Name(s):	Brodalumab
Application Type/Number:	BLA 761032
Applicant/sponsor:	Valeant
OSE RCM #:	2016-1929



EXECUTIVE SUMMARY (place "X" in appropriate boxes)

Memo type					
-Initial			х		
-Interim					
-Final					
Source of safety concern					
-Peri-approval			x		
-Post-approval					
Is ARIA sufficient to help					
characterize the safety concern?					
Safety outcome	SIB	Neutropenia	Serious	Malignancy	MACE
			infections		
-Yes		Inpatient	Serious		MI, stroke
		neutropenia	infections in		
			general		
-No	х	Outpatient	Specific	Х	MACE
		neutropenia	opportunistic		
			infections		CV Death
If "No", please identify the					
area(s) of concern.					
-Surveillance or Study Population					
-Exposure					
-Outcome(s) of Interest		x	x	Х	х
-Covariate(s) of Interest					
-Surveillance Design/Analytic					
Tools					



1 BACKGROUND INFORMATION

1.1 Medical Product

Brodalumab is a human monoclonal antibody that binds to the interleukin-17 (IL-17) receptor A, thus blocking the pro-inflammatory effects of the interleukins IL-17A, IL-17C, IL-17F, IL-17A/F heterodimer, and IL-25. This is thought to be brodalumab's mechanism of action in psoriasis. At present brodalumab is marketed only in Japan. On November 16, 2015, AstraZeneca submitted BLA 761032 for brodalumab in the treatment of moderate to severe plaque psoriasis, in adults who are candidates for systemic therapy or phototherapy. Subsequently, ownership of the BLA was transferred to the current applicant, Valeant. Because of concerns regarding suicidal ideation and behavior (SIB) among clinical trial subjects, clinical trials were halted as of May 2015; accordingly, there are no ongoing clinical trials of brodalumab and no additional clinical trial data is forthcoming at present. Whether conduct of clinical trials will be resumed after market approval remains to be seen.

The memo that follows reflects DEPI-1's thinking and recommendations following discussions held with the DDDP review team and Dr. Michael Nguyen at a Signal Assessment Meeting for brodalumab, 11/16/2016. The safety issues of interest identified by the DDDP review team included infections, malignancy, neutropenia, worsening of Crohn's disease, development of anti-brodalumab antibodies, suicidal ideation and behavior (SIB), and major adverse cardiovascular events (MACE). Of these, worsening of Crohn's disease will be handled with a contraindication in the brodalumab label, and immunogenicity cannot be assessed from healthcare claims data. The remaining safety issues are discussed below.

1.2 Describe the Safety Concerns

1.2.1Suicidal ideation and behavior (SIB)

Six brodalumab-treated trial subjects committed suicide, indicating a rate of suicide in brodalumab trials that was several-fold higher than typically observed in clinical development programs for systemic psoriasis treatments, as described in the DEPI-1 review of 3/22/2016. At this time, the plan is to address this potential risk via an ETASU REMS. In addition, a postmarketing safety clinical trial ^{(b) (5)} is under consideration.

1.2.2 Neutropenia

AstraZeneca's 4 month safety update to the BLA concluded that, "Neutropenia is an identified risk for brodalumab" (page 107). Neutropenia is one of the safety outcomes identified by the DDDP review team as requiring further assessment post-approval. IL-17 has a role in regulating



neutrophil proliferation by stimulating G-CSF,¹ and accordingly neutropenia is a hypothesized adverse effect of brodalumab treatment.

The following data are reproduced from the sponsor's draft labeling, and show the occurrence of the adverse event of neutropenia over 12 weeks of treatment in the pooled clinical trial data.

A

discontinuations of brodalumab treatment, and no cases were associated with severe infections. Overall, in all trials (double blind and open label), 104 out of the 4644 psoriasis subjects receiving brodalumab had neutropenia as an adverse event, equivalent to a rate of 1.2 per 100 person-years of treatment.

1.2.3 Serious infections

Increased susceptibility to infections is regarded as a class effect of psoriasis biologics due to their immunosuppressant effects, and is a labeled risk for the class. As stated in the sponsor's draft label, in 12-week placebo-controlled psoriasis trials, serious infections occurred in 0.5% of brodalumab-treated subjects versus 0.2% of placebo-treated subjects. Among all 4464 psoriasis subjects treated with brodalumab, there were 109 serious infections, representing a rate of 1.2 per 100 person-years of exposure. These 109 serious infections included 2 serious opportunistic infections, 1 crytococcal meningitis and 1 coccidiodomycosis. Comparing serious infection rates among brodalumab-treated psoriasis patients to those seen with other biologics, brodalumab' s rate of 1.2 serious infections per 100 person-years of exposure was not markedly higher than that observed in clinical trials with other products (please refer to the DEPI-1 review of 6/27/2016).² There were no cases of active tuberculosis reported in brodalumab trials, but to the extent that prospective subjects were screened for active/latent tuberculosis, the absence of active tuberculosis cases in brodalumab trials should not be interpreted as evidence that brodalumab does not share this risk with other psoriasis biologics.

1.2.4 Malignancy

(b) (4)



Malignancy is hypothesized to be a potential risk of immunosuppressant therapies for psoriasis. In the brodalumab psoriasis trials, as reported in the 4 month safety update to the BLA, out of 4464 with 9174 subject-years of follow-up, 93 subjects had an adverse event of malignancy. Fifty-six were non-melanoma skin cancers; 37 were other forms of malignancies, representing a rate of roughly 0.4 per 100 person-years. Of these 37, 8 were prostate cancer, 4 were pancreatic cancer, 4 were breast cancer, 4 were colorectal cancer, and the remainder were other varieties of cancer. According to the sponsor's draft labeling, there have been no preclinical carcinogenicity studies of brodalumab.

1.2.5 Major Adverse Cardiovascular Events (MACE)¹

There is evidence that psoriasis is a cardiovascular risk factor; a meta-analysis of six cohort studies found a 25% higher risk for MI in patients with psoriasis versus the general population.³ It has been proposed that IL-17 has a pathogenic role not only in psoriasis but also in atherosclerosis, and that this may be one explanation for the observation that psoriasis is a risk factor for cardiovascular disease. Speculatively, agents active against IL-17 may convey cardiovascular benefits for psoriasis patients.⁴ However, data submitted with the BLA indicate that brodalumab treatment raises circulating IL-17A concentrations, which could mean that brodalumab treatment might accelerate atherosclerosis and thereby increase the incidence of MACE. In controlled portions of trials with brodalumab, events of MACE were too sparse for meaningful comparisons to placebo or active controls. Please see the table below, reproduced from the DEPI-1 review of MACE.⁵

¹ Nonfatal stroke, nonfatal myocardial infarction, or cardiovascular death



L.	12-week placebo controlled		52 week active controlled		All psoriasis Phase 3 brodalumab subjects		
	Placebo	Ustekinumab	Brodalumab	Ustekinumab	Brodalumab (includes follow-up person time)	Brodalumab (includes follow-up person time)	Brodalumab, exposed person time only
N	842	613	2908	613	3828	4273	4273
Person years (pyr)	-	-	-	511.0	3378.3	8365.2	7870.4
MACE	0	0	3	2	24	54	40
CV death	0	0	0	1	3	12	5
MI	0	0	2	1	16	30	25
Stroke	0	0	1	0	5	12	10
MACE/1000 pyr (95% CI)	-	-		3.9 (0.5, 14.1)	7.1 (4.6, 10.6)	6.5 (4.8, 8.4)	5.1 (3.6, 6.9)
CV death/1000 pyr (95% CI)	-	-	-	2.0 (0.05, 10.9)	0.9 (0.2, 2.6)	1.4 (0.7, 2.5)	0.6 (0.2, 1.5)
MI/1000 pyr (95% CI)			-	2.0 (0.05, 10.9)	4.7 (2.7, 7.7)	3.6 (2.4, 5.1)	3.2 (2.1, 4.7)
Stroke/1000 pyr (95% CI)	-	-	-	0 (0, 7.2)	1.5 (0.5, 3.5)	1.4 (0.7, 2.5)	1.3 (0.6, 2.3)

Comparing MACE rates among all brodalumab-treated psoriasis patients to those seen in development programs for other psoriasis biologics, brodalumab had a rate of MACE of 6.5 per 1000 person years, numerically higher than that seen in other psoriasis biologics development programs (DEPI-1 review⁵). A consultation from DCRP⁶ concluded that the existing brodalumab clinical trial data do not establish an elevated risk for MACE. Accordingly, the MACE risk may be viewed as hypothetical at this time, as the cardiovascular effects of elevated IL-17 levels are not well understood. Though DCRP deemed the data on MACE inconclusive overall, the DCRP consult noted that there were 5 sudden cardiovascular deaths among brodalumab-treated subjects, some at relatively young ages (only 2 were > 65 years old). Thus, sudden cardiovascular death would be an important component of any post-marketing risk assessments addressing MACE.

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

Purpose (place an "X" in the appropriate boxes; more than one may be chosen)					
	SIB	Neutropenia	Serious	MACE	Malignancy
			Infection		
Assess a known serious risk					
Assess signals of serious risk					
Identify unexpected serious risk when	х	х	х	x	х
available data indicate potential for					
serious risk					



1.4 Statement of Purpose

This Active Risk and Identification Analysis (ARIA) Sufficiency Memo considers whether ARIA may be used in the postmarketing environment to assess brodalumab's association with each of the aforementioned potential safety risks (SIB, neutropenia, serious infections, malignancy, MACE). The existing clinical trial data do not establish a causal relationship to brodalumab for any of these adverse outcomes, but all may be considered at least theoretical serious risks of brodalumab treatment based on the data from clinical trials and/or extrapolation from other psoriasis biologic products. The table in section 1.3 above provides specific purposes by specific safety outcome.

The purpose of any such ARIA analyses in a regulatory context would be to provide a quantification of the purported risks, using post-marketing surveillance, that would be suitable for inclusion in labeling. If a significant risk is found, a REMS might be considered.

1.5 Effect Size of Interest or Estimated Sample Size Desired

ARIA is under consideration for these safety outcomes from the standpoint of post-marketing surveillance, rather than for use in a hypothesis-driven study. Thus, there are no *a priori* levels of risk to rule in or out for the safety outcomes of interest, versus other psoriasis biologics, as there might be in a protocol-based assessment. With respect to the sample size desired, we note that the brodalumab clinical trial database included 4464 psoriasis subjects treated with brodalumab, for a total duration of exposure of 9174 person-years. It seems reasonable to aim for exceeding the sample size and person-time in the clinical trial database, though setting precise requirements for the person-time and number of exposed subjects needed for an ARIA would be speculative.

2 SURVEILLANCE OR DESIRED STUDY POPULATION

2.1 Population

At the time of writing, the intention is to indicate brodalumab for the treatment of moderate to severe plaque psoriasis in adults who require systemic therapy but have not responded to other systemic psoriasis therapies. Thus, a population of such patients would be the target of any ARIA.

However, there may be issues with sufficient market uptake given the anticipated boxed warning and ETASU REMS to address SIB, and the availability of a number of other efficacious biologics.

2.2 Is ARIA sufficient to assess the intended population?

We anticipate that any brodalumab users captured in the Sentinel database will belong to the population defined by its approved indication, as one of the goals of the ETASU REMS will be to ensure that is the case. Thus, off-label use should not complicate obtaining an appropriate sample of brodalumab users via ARIA. However, identifying a comparable patient population using other psoriasis systemic therapies will be challenging, if possible at all. Brodalumab will be intended for



patients who are candidates for systemic therapy who have failed other psoriasis biologic therapies. Thus, any comparisons of brodalumab users to users of other psoriasis biologics will need to come with the caveat that the patient populations are probably not comparable, and that brodalumab-treated subjects are likely to have more severe or more refractory psoriasis. This might be mitigated by attempting to identify a group of patients treated with the comparator who have a record of being prescribed other systemic therapies for psoriasis.

3 EXPOSURES

3.1 Treatment Exposure(s)

Patients receiving brodalumab can be readily identified in health care claims data, in both inpatient and outpatient settings using coded information.

3.2 Comparator Exposure(s)

Similarly, health care claims data available for ARIA should be sufficient for defining exposure to other psoriasis biologics that would serve as comparators, in both inpatient and outpatient settings using coded information .

3.3 Is ARIA sufficient to identify the exposure of interest?

Coded information in the inpatient setting may not be available for injections during hospitalization, and prescription data only indicates that a prescription was filled, not necessarily administered. Despite these issues, the risk of any bias would be likely low, so ARIA should be sufficient for defining exposure to brodalumab.

4 OUTCOME(S)

4.1 Outcomes of Interest

4.1.1 SIB

Suicidal ideation and behavior may be defined as including completed suicide, suicide attempt, preparatory acts toward imminent suicidal behavior, and suicidal ideation.⁷

4.1.2 Neutropenia

Neutropenia is defined by the absolute neutrophil count (ANC) per microliter, with mild neutropenia typically considered to indicate an ANC <1500, moderate neutropenia an ANC <1000, and severe neutropenia an ANC <500.



According to OSE's Sentinel ARIA Sufficiency Template Guidelines dated 2/10/2016, outcomes with an algorithm requiring laboratory values are designated as "not currently supported by existing data and tools" for ARIA. Neutropenia that results in hospital treatment can be captured in Sentinel (though this would overlap somewhat with the outcome of serious infection), and a previous study showed hospitalized neutropenia in health care claims data has good positive predictive value (97%).⁸ However, not all febrile patients with neutropenia necessarily receive inpatient care,⁹ so requiring hospitalization as part of the outcome definition may overlook relevant cases and so reduce sensitivity. That said, one recent study showed that outpatient diagnostic codes for neutropenia in claims data have limited validity in the absence of laboratory data,¹⁰ so it would not be desirable to include outpatient diagnoses to improve sensitivity.

4.1.3 Serious infections

Serious infection may be defined as an infection that is a serious adverse event; an operational definition for the purpose of this ARIA assessment would be an infection that requires hospitalization. A subset of serious infections are serious opportunistic infections, caused by pathogens to which immunosuppressed patients are especially vulnerable. Serious infections were not an outcome evaluated as part of Sentinel's Health Outcome of Interest Validations and Literature Reviews.¹¹ A recent systematic review of the validity of serious infection diagnostic codes in healthcare claims data found mixed results for the performance of case definition algorithms across 24 studies.¹²

4.1.4 Malignancy

There is at present no specific signal for any individual type of malignancy associated with brodalumab treatment. Thus, the outcome of malignancy for this ARIA assessment may be considered to include all malignancies, and more specifically malignancies excluding nonmelanoma skin cancers. Validity of malignancy outcomes was not assessed in the aforementioned Sentinel Health Outcome of Interest Validations and Literature Reviews. However, a validation study of a variety of malignancy diagnoses in Medicare data found good specificities (at least 98%) and sensitivities of 40-90%; though the positive predictive values varied according to the type of malignancy, being lowest for leukemia.¹³ Accordingly, depending on the type of malignancy of interest, healthcare claims data may be acceptable. Another limitation is that diagnostic codes for malignancies in claims data do not convey all the clinical characteristics that may be of interest, such as would be available from a cancer registry. However, an even more fundamental concern regarding the sufficiency of ARIA to assess malignancy outcomes is the duration of follow-up available in the Sentinel distributed database in the context of the regulatory need. The following figure displays the numbers of patients by length of follow-up data available. Roughly ³/₄ of all patients in the database have at most 3 years of follow-up information available. While the pattern of follow-up time available in the future may only be guessed, the relatively short follow-up times



for the vast majority of patients currently is not promising for future analyses of long-term outcomes such as malignancy. In the postmarketing studies requested for assessment of malignancy with other psoriasis biologics, ixekizumab and secukinumab, 8 years of follow-up was recommended.^{14,15}

Figure 1. Number of Enrollment Records by Length of Enrollment and Number of Contributing Data Partners, Sentinel Distributed Database (source: ARIA Sufficiency Memo for Ocrelizumab, 11/15/2016)



4.1.5 MACE

Major adverse cardiovascular events were defined by the sponsor as including myocardial infarction (MI), stroke, and cardiovascular death (see 4-month safety update, Section 2.7.6), and also identified by DDDP as an outcome of interest important for post-marketing assessment.

A Mini-Sentinel validation project for acute myocardial infarction¹⁶ found that the positive predictive value (PPV) for ICD9 principal or first-listed discharge codes 410.x0 or 410.x1 (excluding 410.x2, which indicates a past MI) in healthcare claims was 86%. Thus, ARIA may be considered adequate for identifying acute hospitalized MI in claims data.



A systematic review of the validity of algorithms for identifying stroke in health care claims data, which was sponsored by the Mini-Sentinel project, found PPVs generally \geq 80% for ICD9 codes 430.x, 432.x or 434.x.¹⁷ Thus, while there are a number of specific case definitions that can be used, ARIA may also be considered adequate for identifying the nonfatal stroke component of MACE.

However, ARIA would not be as successful at identifying fatal cardiovascular events in cases where the death occurred outside of the hospital, notably out-of-hospital sudden cardiac death. This is a well-known limitation of healthcare claims databases and stems from the absence of a code for a medical encounter in cases where the decedent receives no medical care.

4.2 Is ARIA sufficient to assess the outcome of interest?

4.2.1 SIB

OSE is currently evaluating methods for identifying suicidal outcomes in health care claims data.¹⁸ A previous review of this outcome under the MiniSentinel project, conducted by researchers outside of FDA and published in 2012, concluded that "…insufficient data currently exist to make definitive recommendations regarding a preferred algorithm" for identifying suicides and suicide attempts in such databases. Among other issues, suicidal ideation, suicide attempts, or completed suicides may not reliably generate claims for health care encounters with relevant diagnostic codes.

Accordingly, ARIA is not deemed sufficient to assess SIB as an outcome. It should be noted that at the current time, it is likely that SIB cannot be addressed by any observational study using claims data.

4.2.2 Neutropenia

On balance, for the reasons outlined in Section 4.1.2 above, ARIA is not deemed sufficient for the outcome of neutropenia overall, but would be sufficient for an outcome of hospitalized neutropenia given that its positive predictive value is expected to be high in healthcare claims data.

4.2.3 Serious infection

Similar to the finding of a recent DEPI-1 ARIA Sufficiency Memo for ustekinumab (8/19/2016), ARIA is sufficient for assessing serious infections broadly defined, but would be of uncertain utility for assessing serious opportunistic infections specifically. Accordingly, an association with one specific type of serious infection could be missed.

4.2.4 Malignancy

As noted above, current postmarketing studies for other biologics for this indication are recommending 8 years of follow-up, however currently in Sentinel less than 4% of the population



has sufficient follow-up time. Accordingly, ARIA is deemed insufficient for both monitoring for malignancy long after first exposure to brodalumab, as well as evaluating for the risk of long-term exposure to brodalumab.

4.2.5 MACE

As noted above, MACE has three main components, MI, stroke, and cardiovascular death. Although ARIA could likely identify stroke or MI adequately, which are important components of MACE, ARIA is currently unable to reliably identify sudden cardiovascular deaths occurring outside the hospital. Thus, if MACE is the concern, the inadequacy of data on sudden cardiovascular death renders ARIA insufficient for MACE. For the separate sub-components, that have been secondary outcomes of interest for PMR studies of recently approved products,^{19,20} ARIA can address the sub-components, of AMI and Stroke, however ARIA cannot address cardiovascular death occurring outside the healthcare system.

5 COVARIATES

5.1 Covariates of Interest

The covariates of interest are the baseline demographic and clinical characteristics of the users of brodalumab or comparator treatments that could influence the risk of having one of the targeted outcomes. These would include the broad range of medical comorbidities and concomitant medications, and may differ somewhat by the particular outcome to be assessed. Concerns about specific covariates of interest are noted in the following section.

5.2 Is ARIA sufficient to assess the covariates of interest?

Generally speaking, health care claims data can identify many, if not most, covariates relevant for the assessment of the safety outcomes considered here. One important exception worth noting is the lack of information on smoking history which is of course a risk factor for MACE. Other cardiovascular risk modifying factors not transparent to ARIA include use of over-the-counter low dose aspirin for cardioprotection and body mass index. For malignancy, family history is not ascertainable with ARIA. Another limitation with respect to covariates is the incompleteness of data on comorbidities by virtue of relatively short look-back periods for some patients in the database (see the discussion of length of follow-up time, above). However, these are common weaknesses of analyses using claims data, and would not necessarily preclude use of ARIA.

6 SURVEILLANCE DESIGN / ANALYTIC TOOLS

6.1 Surveillance or Study Design

For the safety outcomes considered, a simple "one-armed" surveillance to determine the rate of events of interest among brodalumab users would not be very informative as these events are not



rare in the population of psoriasis patients. To be informative, events with a comparator exposure would need to be assessed as well; the most logical comparator would be another psoriasis biologic, which would provide some comparability regarding severity of psoriasis. The existing ARIA regression tools for propensity score adjustments would need to be employed to enhance comparability of the brodalumab and the comparator samples.

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

ARIA analytic tools should be sufficient to assess the question of interest, particularly since propensity score methods can be used to guard against gross heterogeneities between patients receiving brodalumab and the comparator. However, there are two important caveats.

1. Brodalumab will be approved with a restricted indication, the exact wording of which is not finalized, but the essential concept is that because of the potential association with suicide, brodalumab should be reserved for patients for whom there is no reasonable alternative therapy. The ETASU REMS will be in place to ensure awareness of this. Additionally, the label will recommend discontinuation in the absence of efficacy after a certain period of time. These factors will likely set brodalumab usage apart from other treatments. Even with sophisticated analytic tools it may not be possible to identify samples of patients using brodalumab and the chosen comparator that are truly comparable. For MACE in particular, for which psoriasis is a risk factor, disparities in duration or severity of disease may influence the observed event rates.

2. A sufficient sample of brodalumab users will be required for any ARIA analyses of these safety outcomes, regardless of the specific analytic tools employed. While available data do not permit specific power or sample size calculations, poor market uptake of brodalumab (which is predicted based on the restrictions under which it will be approved) will limit the ability to conduct an ARIA for any of the safety outcomes discussed. That said, the same difficulty will complicate efforts to enroll subjects in any open label clinical trials or registries designed to examine these safety outcomes.

7 NEXT STEPS

7.1 SIB

No postmarketing observational studies are recommended at this time to assess the risk of suicide with brodalumab. Requiring a postmarketing clinical trial (b) (5) is being considered at this time.

7.2 Neutropenia


As ARIA will not be sufficient to evaluate this safety outcome, because of the need for laboratory values, a study incorporating access to laboratory values may be considered. This could be an open label clinical trial, a prospective cohort study, a large simple safety trial, or a retrospective observational study in a database providing laboratory values. However, for neutropenia resulting in hospitalization, ARIA may be sufficient, and a feasibility analysis would be the next step.

7.3 Serious infection

ARIA is considered sufficient for the assessment of serious infections broadly defined. Accordingly, the next step would be to conduct a feasibility analysis to assess brodalumab' s market uptake and the resulting sample size and person-time available for analysis using ARIA. Other avenues, such as prospective cohort study, should be considered if the goal is to assess the risk of specific opportunistic infections that may not be well captured in claims data.

7.4 Malignancy

ARIA is not considered sufficient for the assessment of an association of brodalumab with malignancies. Because of the long-term follow-up needed for assessment of cancer risk, clinical trial data will be of limited value. A prospective cohort study of brodalumab users would offer the best chance of adequately assessing cancer risk.

7.5 MACE

ARIA is deemed insufficient to address MACE and its sub-component of cardiovascular death., specifically sudden cardiac death. Accordingly, other methods should be considered for assessment of MACE; e.g., prospective cohort study, observational studies in databases that can capture sudden cardiac death.

However, ARIA is considered sufficient for the MACE subcomponents 1) acute MI and 2) stroke. As with serious infections, the feasibility of ARIA for this purpose will be governed by the available sample size.

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/s/

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

FINAL LABEL AND LABELING REVIEW

Date:	December 16, 2016
Reviewer:	Jibril Abdus-Samad, PharmD, Labeling Reviewer
	Office of Biotechnology Products (OBP)
Through:	Willie Wilson, PhD, Quality Reviewer
	OBP/Division of Biotechnology Review and Research I
Application:	BLA 761032/0
Product:	Siliq (brodalumab)
Applicant:	Valeant Pharmaceuticals Luxembourg S.a.r.l. (VPL)
Submission Dates:	November 16, 2015; June 17; December 13, 2016

Executive Summary:

The container label and carton labeling for Siliq (brodalumab) Injection 210 mg/1.5 mL in a prefilled syringe submitted on December 13, 2016 is acceptable. If approved, the Agency will assign a U.S. license number to the Applicant because this will be their first approved BLA. Prior to printing, the Applicant must add their assigned U.S. license number to the manufacturer information in their labeling.

Background and Summary Description:

The Applicant submitted 351(a) BLA 761032 Siliq (brodalumab) on November 16, 2015. The Applicant submitted labeling on November 16, 2015. Subsequent to an April 1, 2016 change in Applicant from AstraZeneca UK Ltd to Valeant Pharmaceuticals Luxembourg S.a.r.l. (VPL). On June 17, 2016 the Applicant submitted new container label and carton labeling reflecting the new Applicant appearing on the labeling. Table 1 lists the proposed characteristics of Siliq (brodalumab).

Proprietary Name:	Siliq
Proper Name:	brodalumab
Indication:	human interleukin 17 Receptor A (IL-17RA) antagonist, indicated for the treatment of moderate to severe plaque psoriasis in adult patients who are candidates for systemic therapy or phototherapy.
Dose:	210 mg by subcutaneous injection at weeks 0, 1, and 2 followed by every 2 weeks.
Route of Administration:	Subcutaneous injection
Dosage Form:	Injection
Strength and Container- Closure:	210 mg/1.5 mL single-dose prefilled syringe
Storage and Handling:	Store refrigerated at 2°C to 8°C (36°F to 46°F) in the original carton ^{(b) (4)} prefilled syringes can be stored at room temperature between 68°F to 77°F (20°C to 25°C) in the original carton for a maximum single period of 14 days with protection from light and sources of heat. Once the prefilled syringe has reached room temperature, it should not be placed back into the refrigerator. If not used within 14 days at room temperature, the prefilled syringe should be discarded. Keep in original carton to protect from light and physical damage during storage. Keep out of the sight and reach of children. Do not freeze. Do not shake.

Table 1: Proposed Product Characteristics of Siliq (brodalumab).

Materials Reviewed:

Container Label submitted June 17, 2016 Carton labeling submitted June 17, 2016 Start of Sponsor Material

Container Label

(b) (4)

End of Sponsor Material

Subpart G-Labeling Standards Subpart A-General Labeling Provisions

I. Container

A. 21 CFR 610.60 Container Label

(a) Full label. The following items shall appear on the label affixed to each container of a product capable of bearing a full label: *not applicable. The container label is a partial label; however there may be space to add some additional information.*

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

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

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

> OBP Request: Relocate the dosage form "Injection" to appear under the proper name. This is the appropriate position of the dosage form for CDER regulated specified biologics. *Applicant revised as requested*.

• the lot number or other lot identification; conforms.

• the name of the manufacturer; *does not conform*.

OBP Request: Revise the manufacturer information so that the Applicant/licensed manufacturer "Valeant Pharmaceuticals Luxembourg S.a.r.l." appears as "Manufactured by." For partial labels, only the manufacturer name is required. If there is space, you may include the license number. For example:

Manufactured by: Valeant Pharmaceuticals Luxembourg S.a.r.l. *Applicant revised as requested*.

- in addition, for multiple dose containers, the recommended individual dose; *not applicable, single-dose product*.
- Containers bearing partial labels shall be placed in a package which bears all the items required for a package label; *conforms*.

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

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

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

C. 21 CFR 201.5 Drugs; adequate directions for use; conforms.

D. 21 CFR 201.6 Drugs; misleading statements; conforms.

E. 21CFR 201.10 Drugs; statement of ingredients; placement and prominence; *not applicable on a partial label.*

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

OBP Request: Relocate the route of administration "For Subcutaneous Use Only" to appear under the strength statement "210 mg/1.5 mL." *Applicant revised as requested*.

- G. 21 CFR 201.17 Drugs; location of expiration date; conforms.
- H. 21 CFR 201.25 Bar code; not applicable for partial labels.
- I. 21 CFR 201.50 Statement of identity; conforms.

J. 21 CFR 201.51 Declaration of net quantity of contents; does not *conforms*.

We find the total drug delivered per the total volume should represent the strength. Based on USP General Chapters <7> Labeling, the strength per mL is typically required when the volume is greater than 1 mL. However, considering the total contents of this PFS are intended for administration and there are no partial dosing or syringe markings, we recommend omitting the strength per mL.

OBP Request: Revise the prominent strength statement to include a space between the number and the unit of measure (i.e. 210 mg/1.5 mL) to improve legibility. *Applicant revised as requested*.

- K. 21 CFR 201.55 Statement of dosage; not applicable for partial labels.
- L. 21 CFR 201.100 Prescription drugs for human use; conforms.

Start of Sponsor Material	
Carton Labeling	
	(b) (4)

End of Sponsor Material

II. Carton

A. 21 CFR 610.61 Package Label:

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

OBP Request: Relocate the dosage form "Injection" to appear under the proper name. This is the appropriate position of the dosage form for CDER regulated specified biologics.

Applicant revised as requested.

b) The name, addresses, and license number of manufacturer; *does not conform*.

OBP Request: Revise the manufacturer information so that the Applicant/licensed manufacturer "Valeant Pharmaceuticals Luxembourg S.a.r.l." appears as "Manufactured by." For example:

Manufactured by: Valeant Pharmaceuticals Luxembourg S.a.r.l. Grand Duchy of Luxembourg, L-1931, Luxembourg US License number xxxx *Applicant revised as requested*.

- c) The lot number or other lot identification; *conforms*.
- d) The expiration date; *conforms*.

e) The preservative used and its concentration, if no preservative is used and the absence of a preservative is a safety factor, the words "no preservative" *conforms*.

f) The number of containers, if more than one; conforms.

g) The amount of product in the container expressed as (1) the number of doses, (2) the volume, (3) units of potency, (4) weight, (5) equivalent volume (for dried product to be reconstituted), or (6) such combination of the foregoing as needed for an accurate description of the contents, whichever is applicable; *does not conform.*

OBP Request: Revise the prominent strength statement within the orange circle "210 mg" to read "210 mg/1.5 mL". *Applicant revised as requested*.

h) The recommended storage temperature; *does not conform*. *The labeling lacks storage instructions for room temperature storage and a place for end-users to write the date removed from the refrigerator*.

> OBP Request: We note the room temperature storage instructions appear in the instructions for use (IFU). However, the carton labeling lacks this information. Additionally, there is no method for end-users to track when they removed the product from refrigerator storage. Therefore, revise the storage instructions to include room temperature storage instructions that appear in the IFU.

Store refrigerated at 2°C to 8°C (36°F to 46°F) in the original carton to protect from light. Do not freeze. Do not shake.

When necessary, SILIQ can be stored at room temperature up to a maximum of 77°F (25°C) in original carton for a maximum single period of 14 days with protection from light and sources of heat. Once SILIQ reaches room temperature, do not place back in refrigerator. Discard after 14 days at room temperature.

Date removed from refrigerator ___/___/

Applicant revised as requested.

i) The words "Do not Freeze" or the equivalent, as well as other instructions, when indicated by the character of the product; *conforms*.

j) The recommended individual dose if the enclosed container(s) is a multiple-dose container; *not applicable, single-dose product*.

k) The route of administration recommended, or reference to such directions in and enclosed circular; *conforms*.

I) Known sensitizing substances, or reference to enclosed circular containing appropriate information; *not applicable.*

m) The type and calculated amount of antibiotics added during manufacture; *not applicable.*

n) The inactive ingredients when a safety factor, or reference to enclosed circular containing appropriate information; *not applicable*.

o) The adjuvant, if present; not applicable.

p) The source of the product when a factor in safe administration; *not applicable.*

q) The identity of each microorganism used in manufacture, and, where applicable, the production medium and the method of inactivation, or reference to an enclosed circular containing appropriate information; *not applicable.*

r) Minimum potency of product expressed in terms of official standard of potency or, if potency is a factor and no U.S. standard of potency has been prescribed, the words "No U.S. standard of potency"; *conforms*.

- s) The statement "Rx only" for prescription biologicals; *conforms*.
 - Note: If product has a medication guide, a statement is required on the package label if it is not on the container label (see above). It is recommended on both labels.

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

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

D. 21 CFR 610.64 Name and address of distributor; *does not conform*.

The name and address of the distributor of a product may appear on the label provided that the name, address, and license number of the manufacturer also appears on the label and the name of the distributor is qualified by one of the following phrases: "Manufactured for _____". "Distributed by _____", "Manufactured by _____ for ____", "Manufactured for _____ by ____", "Distributor: _____", or 'Marketed by _____". The qualifying phrases may be abbreviated. OBP Request: Per 21 CFR 610.64, you may include a distributor provided you labeled the Applicant's name, address, and license number. *Applicant revised as requested*.

E. 21 CFR 610.67 Bar code label requirements: conforms.

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

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

G. 21 CFR 201.5 Drugs; adequate directions for use; conforms.

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

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

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

OBP Request: Relocate the route of administration to appear under the strength statement.

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

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

M. 21 CFR 201.50 Statement of identity; conforms.

N. 21 CFR 201.51 Declaration of net quantity of contents; *does not conforms.*

OBP Request: Revise the prominent strength statement within the orange circle "210 mg" to read "210 mg/1.5 mL". *Applicant revised as requested*.

O. 21 CFR 201.55 Statement of dosage; conforms.

P. 21 CFR 201.100 Prescription drugs for human use; *conforms*. However we recommend revising the list of ingredients to appear as:

OBP Request: Revise the list of ingredients by listing the amounts delivered in 1.5 mL. For example:

Each single-dose prefilled syringe delivers 1.5 mL of solution containing brodalumab 210 mg, glutamate (6.5 mg), polysorbate 20 (0.15 mg), proline (36 mg), and Water for Injection. *Applicant revised as requested*.

Conclusions:

The container label and carton labeling for Siliq (brodalumab) 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), [USP 39/NF 34 December 1, 2016 to April 30, 2017]. Labeling deficiencies were identified and resolved. The container label and carton labeling submitted on December 13, 2016 is acceptable (see next page). If approved, the Agency will assign a U.S. license number to the Applicant because this will be their first approved BLA. Prior to printing, the Applicant must add their assigned U.S. license number to the manufacturer information in their labeling.





Jibril Abdus-Samad



Digitally signed by Jibril Abdus-Samad Date: 12/16/2016 03:14 26PM GUID: 50814c7000007a3754a457f037f74915

Digitally signed by Willie Wilson Date: 12/16/2016 03:19:41PM GUID: 542e18bc000444f367cd79bb56beba7a

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

OSE RCM #	2015-2628
Reviewer Name(s)	Erin M. South, Pharm.D. Ana Tavakoli, M.A.
Team Leader (Acting)	Donella Fitzgerald, Pharm.D.
Deputy Division Director (Acting)	Jamie Wilkins Parker, Pharm.D.
Review Completion Date	December 12, 2016
Subject	Review of REMS Proposal
Established Name	Brodalumab
Applicant	Valeant Pharmaceuticals
Application Number	761032
Therapeutic Class	Interleukin (IL)-17A antagonist
Formulation(s)	210 mg/1.5 mL single-use pre-filled syringe (140 mg/mL)
Dosing Regimen	210 mg subcutaneous injection at Weeks 0, 1, and 2, followed by 210 mg every 2 weeks
Proposed Indication(s)	Treatment of adult patients with moderate-to-severe plaque psoriasis who are candidates for systemic therapy or phototherapy

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1 Introduction

This review by the Division of Risk Management (DRISK) evaluates the proposed risk evaluation and mitigation strategy (REMS) for the new molecular entity (NME) Siliq (brodalumab) submitted by the Applicant on November 16, 2015, and amended on February 4, and October 18, 2016. A Biologics Licensing Application (BLA 761032) was submitted by AstraZeneca on November 16, 2015, for the treatment of adult patients with moderate-to-severe plaque psoriasis who are candidates for systemic therapy or phototherapy. The proposed REMS consists of a Medication Guide (MG), elements to assure safe use (ETASU), and a timetable for submission of assessments. This application is under review in the Division of Dermatology and Dental Products (DDDP). Ownership of the application was subsequently transferred from AstraZeneca to Valeant Pharmaceuticals North America, LLC (Valeant) on April 1, 2016.

DRISK and DDDP agree that a REMS is needed to ensure the benefits of Siliq outweigh its risks. The REMS requires elements to assure safe use (ETASU), including health care providers who prescribe the drug are specially certified, pharmacies that dispense the drug are specially certified, and the drug be dispensed to patients with evidence or other documentation of safe-use conditions.

The Applicant was informed of our determination regarding the need for an ETASU REMS in a meeting between the Agency and the Applicant on August 22, 2016. Valeant submitted a REMS amendment to the BLA on October 18, 2016, which is the subject of this review.

2 Background

2.1 PRODUCT INFORMATION

Siliq, a new molecular entity, is a human IgG2 monoclonal antibody (mAb) that binds to the human interleukin-17 receptor A (IL-17RA), preventing IL-17 from activating the receptor, and, therefore, blocks the biological activities of IL-17A, IL-17C, IL-17F, IL-17A/F heterodimer and IL-25. The Applicant-proposed formulation and dosing regimen for Siliq is a 210 mg/1.5 mL single-use prefilled syringe (140 mg/mL), intended for chronic treatment as a 210 mg subcutaneous (SC) injection at Weeks 0, 1, and 2, followed by 210 mg every 2 weeks, and is likely to be administered by patients or caregivers in the home setting. Population-based pharmacokinetic simulations estimate that serum Siliq concentrations for 95% of subjects would drop below the limit of detection approximately 32 days and 63 days after discontinuing treatment with Siliq 140 mg Q2W and 210 mg Q2W, respectively.

The proposed mechanism of action of Siliq is similar to that of another anti-psoriasis mAb, ixekizumab, which, however, binds to IL-17 itself. BLA 125521 for ixekizumab (Taltz) was

approved March 22, 2016, without a REMS, for the treatment of adults with moderate-to-severe plaque psoriasis who are candidates for systemic therapy or phototherapy.

On July 4, 2016, the Japanese Authority approved brodalumab for marketing in Japan. Additionally, the Applicant has submitted a Marketing Authorization Application to the European Medicines Agency (EMA) for brodalumab for the treatment of moderate-to-severe plaque psoriasis in adults.

2.2 **REGULATORY HISTORY**

The following is a summary of the regulatory history for the proposed REMS relevant to this review:

<u>November 16, 2015</u>: AstraZeneca submitted BLA 761032, for the treatment of adult patients with moderate-to-severe plaque psoriasis who are candidates for systemic therapy or phototherapy. The submission included a REMS, consisting of a Medication Guide, communication plan, and timetable for submission of assessments; the goals were to inform healthcare providers about the potential risk of SIB in patients with psoriasis and the importance of proper patient selection, and to educate patients to recognize the signs and symptoms of changes in their mental health, and to seek intervention should such signs emerge.

<u>April 1, 2016</u>: Ownership of BLA 761032 was transferred from AstraZeneca to Valeant Pharmaceuticals, North America LLC.

<u>April 20, 2016</u>: The Mid-Cycle Communication meeting was held between the Agency and the Applicant, during which the Agency communicated that the risk of SIB was still under review.

<u>May 25, 2016</u>: REMS Oversight Committee (ROC) meeting. The ROC concurred with the review team's plan to present varying opinions of the risk of SIB observed in the clinical trials for brodalumab and potential risk management options to address SIB with brodalumab to the Advisory Committee (AC), and recommended that the review team return to the ROC after that presentation.

June 28, 2016: The Late-Cycle Meeting was held between the Agency and Valeant. Valeant was informed that SIB continues to be a review issue and is expected to be the primary focus of the upcoming AC meeting on July 19, 2016. The Agency informed Valeant that discussion of risk management options is ongoing.

<u>July 19, 2016</u>: Meeting of the FDA Dermatologic and Ophthalmic Drugs Advisory Committee (DODAC) was held. The committee unanimously agreed that there was no safety signal for Major Adverse Cardiac Events (MACE). The majority of the committee agreed that the safety signal for SIB was not clear; however, it was noted that clinicians and patients need to be made aware of the possibility of SIB. The committee unanimously agreed that brodalumab should be approved; 4 committee members voted for approval with labeling alone to manage SIB, and 14 members voted for approval with the addition of risk management options for SIB beyond labeling; of those 14, the majority stated that they supported a registry of some type.

<u>August 9, 2016</u>: A second meeting of the ROC was held. The ROC recommended that a REMS with ETASU was necessary for the approval of brodalumab, in order to ensure the benefits of brodalumab outweigh its risks.

<u>August 22, 2016</u>: Valeant was informed, during a teleconference with DRISK and DDDP, that optimized labeling and a REMS with ETASU is required. Valeant was asked to submit a timeline for the submission of their revised REMS.

<u>August 26, 2016</u>: Valeant requested a meeting with DRISK and DDDP to further discuss the Agency's labeling and REMS requirements

<u>August 31, 2016</u>: DRISK and DDDP held a teleconference with Valeant to discuss the labeling and REMS requirements. Valeant was informed that the REMS with ETASU, as described by the Agency during the August 22, 2016 teleconference, includes the minimum risk mitigation elements necessary for approval. Valeant agreed to submit (by no specific date) revised labeling to meet the Agency's requirements and either a revised REMS or their rationale for why they think a REMS with ETASU is not necessary.

<u>September 16, 2016</u>: Valeant submitted their response to the Agency's August 31, 2016 Information Request; the submission included a proposal to revise their original Communication Plan REMS with the addition of patient informed consent administered by the pharmacy.

<u>September 28, 2016</u>: Valeant requested a face-to-face meeting with the Agency to discuss labeling and the REMS.

<u>October 5, 2016</u>: A meeting was held between the Agency, Valeant, and Dr. Mark Lebwohl, a dermatologist who participated in the brodalumab clinical program, to discuss the Agency's REMS requirements. Valeant said they were still considering the Agency's requirements.

October 18, 2016: Valeant submitted an amendment to their REMS proposal.

October 25, 2016: A Major Amendment Acknowledgment letter was issued based on the Applicant's October 18, 2016 submission; the PDUFA goal date was extended by three months, to February 16, 2017.

3 Risk Management Activities Proposed by the Applicant

3.1 REVIEW OF THE APPLICANT'S PROPOSED REMS

On October 18, 2016, the Applicant submitted an amendment to their REMS. The amended REMS document and materials requires additional revisions to be acceptable, including submission of the REMS website screenshots and REMS supporting document, which should detail the REMS assessment plan. In addition to our comments below, edits have been made to the REMS appended materials provided in the attached redlined documents.

3.2 REMS DOCUMENT

The Applicant's proposed REMS document has been revised to include ETASU; however, additional revisions to the REMS document are required for it to be acceptable.

REMS Goals

The Applicant has proposed the following REMS goal: to mitigate the potential risk of suicidal ideations and behavior by:

- Informing prescribers and pharmacists about the potential risk of suicidal ideation and behavior in patients with psoriasis and the observed incidences of SIB with use of brodalumab, the need to counsel patients about the risks, and consideration of referral of patients to a mental health professional
- Informing patients regarding signs and symptoms of suicidal ideation and behavior, new onset or worsening depression, or other emerging mood changes, and to seek intervention should such signs emerge and inform patients that suicidal ideation and behavior have been reported in patients treated with SILIQ.

Reviewer Comment: The REMS goal should be revised to the following:

- The goal of the SILIQ REMS is to mitigate the potential risk of suicidal ideation and behavior (SIB) associated with SILIQ by:
 - Ensuring that prescribers are educated about the potential risk of suicidal ideation and behavior observed with SILIQ therapy and the need to counsel patients about this risk.
 - Ensuring that patients are informed about the potential risk of suicidal ideation and behavior observed with SILIQ therapy and the need to seek medical attention should they experience emergence or worsening of suicidal thoughts and behavior.

Medication Guide

• The Applicant has included a Medication Guide in the proposed REMS.

Reviewer Comment: The Medication Guide is not required as an element of the REMS. It should, however, be retained as a part of the product labeling.

Elements to Assure Safe Use (ETASU)

• The Applicant has proposed ETASU to include: prescriber enrollment (A), pharmacy enrollment (B), and documentation of safe-use conditions (D).

Reviewer Comment: The Agency agrees that the REMS should include the above elements. However, the Applicant's proposed REMS document requires further revision, to be acceptable.

REMS Website

The Applicant's proposed REMS does not include a REMS website.

Reviewer Comment: The revised REMS proposal should include a SILIQ REMS website.

3.3 REMS APPENDED MATERIALS

We have reviewed the following REMS Program materials submitted by Valeant:

- SILIQ REMS Program Healthcare Provider Enrollment Form
- SILIQ REMS Program Pharmacy Enrollment Form
- SILIQ REMS Program Patient-Provider Agreement Form
- SILIQ REMS Program Patient Wallet Card

Reviewer Comments: The appended materials require formatting and content changes. Refer to comments in Section 6.

3.4 REMS SUPPORTING DOCUMENT AND ASSESSMENT PLAN

The Applicant's October 18, 2016 REMS amendment does not include a revised REMS supporting document, which should include the REMS assessment plan, and is required for a complete submission.

Reviewer Comment: The Applicant must submit an amended REMS supporting document, which should include the below REMS assessment plan. Refer to comments in Section 6.

REMS Assessment Plan

1. **Siliq Stakeholder data** (prescribers, pharmacies, patients, and distributors) per reporting period and cumulatively:

- a. Numbers of each certified/enrolled stakeholder, status of certification, and method of certification including:
 - i. Number of certified prescribers by medical degree, prescriber specialty, and method of certification (email, fax, online)
 - ii. Number of certified pharmacies by pharmacy type (inpatient, outpatient chain, outpatient independent) and method of certification (email, fax, online)
 - iii. Number of authorized distributors and wholesalers
 - iv. Number of enrolled patients and their demographics (age, gender, race)
- b. Listing and categorization of reasons enrollment is incomplete for each stakeholder category.
- 2. **Utilization Data,** per reporting period and cumulatively: Number of Siliq prescriptions (new and refills) dispensed stratified by:
 - a. pharmacy type
 - b. method of dispensing authorization (on-line versus phone)
 - c. prescriber specialty
 - d. patient demographics (age, gender, race)
- 3. Compliance Metrics, per reporting period:
- a. Report of annual audit findings from a representative sample of 25% of certified pharmacies or one, whichever is greater, for audits conducted during the reporting period, including:
 - i. What processes and procedures the REMS and distributors/wholesalers have in place to verify, prior to dispensing Siliq, that the pharmacies are certified
 - ii. What any corrective actions taken to address findings of non-compliance
 - iii. The status of corrective actions,
 - iv. Any resulting preventative actions taken.
 - b. Report of findings from an audit of 25% of the certified pharmacies or one, whichever is greater, within 90 calendar days after the pharmacy places its first order of Siliq to ensure that all processes and procedures are in place and functioning
 - i. This report is to include any corrective actions taken to address findings, the status of corrective actions, and any resulting preventative actions taken
 - c. Number of Siliq prescriptions dispensed that were written by non-certified prescribers and the actions taken to prevent future occurrences.
 - d. Number of Siliq prescriptions dispensed by non-certified pharmacies and the actions taken to prevent future occurrences.
 - e. Number of times a Siliq prescription was dispensed because a certified pharmacy bypassed REMS authorization processes, to include a description of how the events were identified and any corrective actions taken.

- f. Number of shipments sent to non-certified pharmacies, sources of the reports, and actions taken to prevent future occurrences.
- g. Number of prescribers, pharmacies and distributors de-certified and reasons for decertification.
- h. The number of and reasons for rejected prescription authorizations
- i. Failures of Rx dispensing authorization due to calls to the REMS for authorization when the call center was closed or when the prescriber/patient verification portion of the website was down
- j. The numbers of the most frequently asked questions to the Call Center organized by topic.

4. REMS Program implementation (to be provided in the 12 month assessment only)

- a. Product Launch Date
- b. Date when the Siliq REMS website went live
- c. Date healthcare providers could become certified online, by email, or by fax
- d. Date when the REMS Program Website & call center are fully operational, including the online confirmation of patient authorization functionality and the availability of REMS materials

5. Evaluation of knowledge via Knowledge, Attitude and Behavior (KAB) surveys

A. Prescribers

i. An evaluation of knowledge of certified prescribers of the potential risk of suicidal ideation and behavior observed with Siliq therapy.

ii. An evaluation of prescriber practice or behavior with regards to counseling patients about the potential risk of suicidal ideation and behavior observed with Siliq therapy and patients' need to seek medical attention should they experience emergence or worsening of suicidal thoughts and behavior.

iii. An evaluation of certified prescriber knowledge of Siliq REMS requirements and processes.

B. Patients

i. An evaluation of knowledge of patients of the potential risk of suicidal ideation and behavior observed with Siliq therapy and patients' need to seek medical attention should they experience emergence or worsening of suicidal thoughts and behavior.

ii. An evaluation of patients' recall of counseling by prescriber, pharmacist, or both, on the potential risk of suicidal ideation and behavior observed with Siliq therapy and patients' need to seek medical attention should they experience emergence or worsening of suicidal thoughts and behavior.

iii. An evaluation of patient receipt of the wallet card.

C. Pharmacies

i. An evaluation of knowledge of authorized representatives and staff pharmacists in certified pharmacies of the of the potential risk of suicidal ideation and behavior observed with Siliq therapy and patients' need to seek medical attention should they experience emergence or worsening of suicidal thoughts and behavior.

ii. An evaluation of knowledge of authorized representatives and staff pharmacists in certified pharmacies of the Siliq REMS requirements and processes.

DRISK agrees with the proposed frequency of assessments. Refer to comments in Section 6.

4 Discussion

The Applicant's REMS proposal, as submitted on October 18, 2016, includes the Agency's required ETASU. The REMS document and REMS appended materials require significant revisions to be acceptable. Additionally, the proposal should include a REMS website and revised REMS supporting document, which should include the REMS assessment plan, in order for the proposal to be considered complete.

5 Conclusion & Recommendations

DRISK does not find the Applicant's proposed REMS acceptable. Comments for the Applicant are provided in Section 6.

6 Comments for the Applicant

The comments in the attached redlined documents are based on the Agency's review of the proposed REMS for Siliq submitted under BLA 761032. In order to facilitate further review, we ask that you respond to these comments within 7 calendar days, by COB December 19, 2016.

A. General Comments

We have provided revised REMS materials (appended materials, supporting document) which should be submitted as separate documents in the same submission. Submit both a Word tracked changes version and a Word clean version of each of these documents, as well as a .pdf version of each of the previously mentioned documents and appended materials. We ask that you respond to these comments and resubmit all documents by December 19, 2016.

B. Medication Guide

Remove the Medication Guide, as it is not required as an element of the REMS. It should,

however, be retained as a part of the product labeling.

C. REMS Document

Significant revisions to the REMS document are necessary, to be acceptable. See attached redlined REMS document, update, and resubmit. Of note, the REMS document continues to undergo final clearance and may require further revision during the course of the review.

- D. REMS Appended Materials
 - 1. <u>SILIQ REMS Program Healthcare Provider Enrollment Form</u> Retitle the form to SILIQ REMS Program Prescriber Enrollment Form. Refer to the attached redlined document for further edits.
 - 2. <u>SILIQ REMS Program Pharmacy Enrollment Form</u> Refer to the attached redlined document for edits. Retain contact information for Pharmacy and Authorized Pharmacy Representative on the back of the form.
 - 3. <u>SILIQ REMS Program Patient-Provider Agreement Form</u> Retitle the form to *SILIQ REMS Program Patient-Prescriber Agreement Form*. Refer to the attached redlined form for further edits. Note that due to the edits, the revised form flows over onto page 2. When resubmitting, reformat to fit on one page.
 - 4. <u>SILIQ REMS Program Patient Wallet Card</u> The patient wallet card should include the indication of the drug and highlight the risks of Siliq as well as information and resources on the management of these risks.
 - 5. SILIQ REMS Website

Create and submit a SILIQ REMS website. All REMS website screenshots and actual layout and content for the SILIQ REMS website should be submitted for review. For ease of review, we request your submission of these materials in Word format, with a screenshot of each web page on the upper half of a page and the corresponding webpage contents typed on the lower half of the page. If this is not possible, submission of website screenshots in .pdf format is acceptable. Your cover letter of your resubmission should include the date by which you anticipate the website to be fully functional (e.g., prescriber enrollment, patient enrollment). Additionally, we recommend the following:

- Ensure the REMS website is independent of any and all links to the promotional and/or commercial website and non-REMS materials about the product. This includes any hyperlinked company logos which could direct consumers to the company's website.
- Do not include a link from the REMS website back to the www.SILIQ.com website. The REMS website should also be accessible directly through a search engine.
- All REMS materials on the REMS website (e.g., REMS enrollment forms) should be downloadable from the REMS website. All REMS materials should be made available on the website for the duration of the REMS.
- We recommend that you include a prominent link on the product website's

homepage (www.SILIQ.com) for REMS materials. This link should direct users to the SILIQ REMS website on which the REMS program is described. The site should include only FDA-approved REMS materials.

- We ask you to use bullets, moderate white space, short line lengths, and few lines of text when possible when developing your website.
- By way of example, the Agency recommends you review a recently approved REMS website such as the SABRIL REMS website, which is in the public domain.
- E. Supporting Document and Assessment Plan

Submit an amended REMS supporting document (including the REMS assessment plan provided below) that aligns with the REMS and all appended REMS materials. Refer to the attached redlined document for further edits and the draft *Guidance for Industry Format and Content of Proposed Risk Evaluation and Mitigation Strategies (REMS), REMS Assessments, and Proposed REMS Modifications* (Section III (B) "Content of the REMS Supporting Document.")

Include an estimate of the number of pharmacies you anticipate will be certified to dispense Siliq; based on this number, propose metrics for your audits of certified pharmacies in terms of both the percentage of pharmacies that would be audited as well as the minimum number of pharmacies that would be audited. Provide a rationale for your choice of percentage and minimum number, and include examples of the application of these metrics using varying estimates of certified pharmacies in the REMS.

REMS Assessment Plan

Siliq Stakeholder data (prescribers, pharmacies, patients, and distributors) per reporting period and cumulatively:

- a. Numbers of each certified/enrolled stakeholder, status of certification, and method of certification including:
 - i. Number of certified prescribers by medical degree, prescriber specialty, and method of certification (email, fax, online)
 - ii. Number of certified pharmacies by pharmacy type (inpatient, outpatient chain, outpatient independent) and method of certification (email, fax, online)
 - iii. Number of authorized distributors and wholesalers
 - iv. Number of enrolled patients and their demographics (age, gender, race)
- b. Listing and categorization of reasons enrollment is incomplete for each stakeholder category.

Utilization Data, per reporting period and cumulatively: Number of Siliq prescriptions (new and refills) dispensed stratified by:

- c. pharmacy type
- d. method of dispensing authorization (on-line versus phone)

- e. prescriber specialty
- f. patient demographics (age, gender, race)

Compliance Metrics, per reporting period:

- k. Report of annual audit findings from a representative sample of 25% of certified pharmacies or one, whichever is greater, for audits conducted during the reporting period, including:
 - i. What processes and procedures the REMS and distributors/wholesalers have in place to verify, prior to dispensing Siliq, that the pharmacies are certified
 - ii. What any corrective actions taken to address findings of non-compliance
 - iii. The status of corrective actions,
 - iv. Any resulting preventative actions taken.
- Report of findings from an audit of 25% of the certified pharmacies or one, whichever is greater, within 90 calendar days after the pharmacy places its first order of Siliq to ensure that all processes and procedures are in place and functioning
 - i. This report is to include any corrective actions taken to address findings, the status of corrective actions, and any resulting preventative actions taken
- m. Number of Siliq prescriptions dispensed that were written by non-certified prescribers and the actions taken to prevent future occurrences.
- n. Number of Siliq prescriptions dispensed by non-certified pharmacies and the actions taken to prevent future occurrences.
- o. Number of times a Siliq prescription was dispensed because a certified pharmacy bypassed REMS authorization processes, to include a description of how the events were identified and any corrective actions taken.
- p. Number of shipments sent to non-certified pharmacies, sources of the reports, and actions taken to prevent future occurrences.
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- s. Failures of Rx dispensing authorization due to calls to the REMS for authorization when the call center was closed or when the prescriber/patient verification portion of the website was down
- t. The numbers of the most frequently asked questions to the Call Center organized by topic.

REMS Program implementation (to be provided in the 12 month assessment only)

- e. Product Launch Date
- f. Date when the Siliq REMS website went live
- g. Date healthcare providers could become certified online, by email, or by fax

h. Date when the REMS Program Website & call center are fully operational, including the online confirmation of patient authorization functionality and the availability of REMS materials

Evaluation of knowledge via Knowledge, Attitude and Behavior (KAB) surveys

A. Prescribers

i. An evaluation of knowledge of certified prescribers of the potential risk of suicidal ideation and behavior observed with Siliq therapy.

ii. An evaluation of prescriber practice or behavior with regards to counseling patients about the potential risk of suicidal ideation and behavior observed with Siliq therapy and patients' need to seek medical attention should they experience emergence or worsening of suicidal thoughts and behavior.

iii. An evaluation of certified prescriber knowledge of Siliq REMS requirements and processes.

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i. An evaluation of knowledge of patients of the potential risk of suicidal ideation and behavior observed with Siliq therapy and patients' need to seek medical attention should they experience emergence or worsening of suicidal thoughts and behavior.

ii. An evaluation of patients' recall of counseling by prescriber, pharmacist, or both, on the potential risk of suicidal ideation and behavior observed with Siliq therapy and patients' need to seek medical attention should they experience emergence or worsening of suicidal thoughts and behavior.

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C. Pharmacies

i. An evaluation of knowledge of authorized representatives and staff pharmacists in certified pharmacies of the of the potential risk of suicidal ideation and behavior observed with Siliq therapy and patients' need to seek medical attention should they experience emergence or worsening of suicidal thoughts and behavior.

ii. An evaluation of knowledge of authorized representatives and staff pharmacists in certified pharmacies of the Siliq REMS requirements and processes.

7 Appendices

- 1. SILIQ REMS document, redlined
- 2. SILIQ REMS Program Prescriber Enrollment Form, redlined
- 3. SILIQ REMS Program Pharmacy Enrollment Form, redlined

- 4. SILIQ REMS Program Patient-Prescriber Agreement Form, redlined
- 5. SILIQ REMS supporting document, redlined

7.1 SUBMISSIONS

- AstraZeneca, Risk Evaluation and Mitigation Strategy for Brodalumab, BLA 761032, November 16, 2015 (Seq. 0000)
 - o Amendment received February 4, 2016 (Seq. 0009)
 - o Amendment received October 18, 2016 (Seq. 0057)
- Valeant, Risk Evaluation and Mitigation Strategy for Brodalumab, BLA 761032, October 18, 2016 (Seq. 0057)

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/s/

ERIN M SOUTH 12/12/2016

JAMIE C WILKINS PARKER 12/12/2016

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:	November 16, 2016
To:	Kendall Marcus, MD Director Division of Dermatology and Dental Products (DDDP)
Through:	LaShawn Griffiths, MSHS-PH, BSN, RN Associate Director for Patient Labeling Division of Medical Policy Programs (DMPP)
	Barbara Fuller, RN, MSN, CWOCN Team Leader, Patient Labeling Division of Medical Policy Programs (DMPP)
From:	Rowell Medina, PharmD, BCPS 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):	SILIQ (brodalumab)
Dosage Form and Route:	injection, for subcutaneous use
Application Type/Number:	BLA 761032
Applicant:	Valeant Pharmaceuticals Luxembourg S.a.r.l. (VPL)

1 INTRODUCTION

On November 16, 2015, AstraZeneca submitted for the Agency's review a Biologics License Application (BLA) 761032 for SILIQ (brodalumab) injection. On April 1, 2016, AstraZeneca transferred all rights and ownership to Valeant Pharmaceuticals Luxembourg S.a.r.l. (VPL). The proposed indication is for the treatment of adult patients 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 19, 2015 for DMPP and OPDP to review the Applicant's proposed Medication Guide (MG) and Instructions for Use (IFU) for SILIQ (brodalumab) injection.

DMPP conferred with the Division of Medication Error, Prevention, and Analysis (DMEPA) and a separate DMEPA review of the IFU was completed on October 10, 2016.

The Risk Evaluation and Mitigation Strategy (REMS) is being reviewed by the Division of Risk Management (DRISK) and will be provided to DDDP under a separate cover.

2 MATERIAL REVIEWED

- Draft SILIQ (brodalumab) injection MG and IFU received on November 16, 2015, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on November 4, 2016.
- Draft SILIQ (brodalumab) injection Prescribing Information (PI) received on November 16, 2015, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on November 4, 2016.

3 REVIEW METHODS

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

Additionally, in 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. The ASCP and AFB recommended using fonts such as Verdana, Arial or APHont to make medical information more accessible for patients with vision loss. We reformatted the MG document using the Arial font, size 10.

In our collaborative review of the MG 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 meet the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)

4 CONCLUSIONS

The MG and IFU are acceptable with our recommended changes.

5 RECOMMENDATIONS

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

Please let us know if you have any questions.

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/s/

ROWELL MEDINA 11/16/2016

SILVIA WANIS 11/17/2016

BARBARA A FULLER 11/17/2016
FOOD AND DRUG ADMINISTRATION Center for Drug Evaluation and Research Office of Prescription Drug Promotion

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

Memorandum

Date:	November 16, 2016
То:	Strother D. Dixon, RPM Regulatory Project Manager Division of Dermatology and Dental Products (DDDP)
From:	Silvia Wanis, PharmD Regulatory Review Officer Office of Prescription Drug Promotion (OPDP)
Subject:	BLA 761032 OPDP labeling comments for SILIQ [™] (brodalumab) injection subcutaneous use

Reference is made to DDDP's November 19, 2015 consult request for OPDP's comments regarding the proposed Package Insert (PI), Medication Guide (MG), Instructions for Use (IFU), and Carton and Container labeling for Siliq.

for

OPDP's comments on the proposed labeling, which are based on the draft version of the PI emailed by Strother D. Dixon on November 4, 2016, are provided below.

OPDP's has reviewed the proposed Carton and Container Labeling submitted by the applicant and available in the EDR at:

http://sharepoint.fda.gov/orgs/CDER-ODEIII-DDDP/Shared%20Documents/Project%20Management/Strother%20Dixon/BLAs/ BLA%20761032/Labeling/Draft%20Carton%20and%20Container%20Labels%20 210%20mg%202%20pre-filled%20syringe.pdf

http://sharepoint.fda.gov/orgs/CDER-ODEIII-DDDP/Shared%20Documents/Project%20Management/Strother%20Dixon/BLAs/ BLA%20761032/Labeling/Draft%20Carton%20and%20Container%20Labels%20 210%20mg%20pre-filled%20syringe.pdf

OPDP does not have any comments on the proposed Carton and Container labels at this time.

OPDP's review and comments on the proposed MG and proposed 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 11/16/2016

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:	October 4, 2016
Requesting Office or Division:	Division of Dermatology and Dental Products (DDDP)
Application Type and Number:	BLA 761032
Product Name and Strength:	Siliq (brodalumab) Injection 210 mg/1.5 mL Prefilled Syringe (PFS)
Product Type:	Single Ingredient, Combination Product
Rx or OTC:	Rx
Applicant/Sponsor Name:	Valeant Pharmaceuticals Luxembourg S.a.r.l.
Submission Date:	November 16, 2015
OSE RCM #:	2016-2611 and 2015-2612
DMEPA Primary Reviewer:	Carlos M Mena-Grillasca, RPh
DMEPA Team Leader:	Mishale Mistry, PharmD, MPH
DMEPA Associate Director for Human Factors:	QuynhNhu Nguyen, MS

1 REASON FOR REVIEW

This review evaluates the applicant's Human Factors (HF) validation study report, the proposed container label, carton labeling, Prescribing Information (PI), and Instructions for Use (IFU) for Siliq (brodalumab) injection (BLA 761032) in responding to the consult request from the Division of Dermatology and Dental Products (DDDP). This is a 351k submission containing a PFS and the drug product Siliq, intended to treat moderate to severe plaque psoriasis.

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.

Table 1. Materials Considered for this Label and Labeling Review					
Material Reviewed	Appendix Section (for Methods and Results)				
Product Information/Prescribing Information	A				
Previous DMEPA Reviews	В				
Human Factors Study	С				
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

The Applicant proposes a standard, single dose, pre-filled syringe (PFS) with a flange extender for Siliq (2.25 mL glass (Type 1) syringe with a staked in place stainless needle). DMEPA did not request that the Applicant conduct a HF validation study for the proposed PFS nor reviewed the HF study protocol. We noted an issue regarding the representativeness of the study participants to the intended users in that all of the participants had high school education or higher, which is not representative of the US literacy level.

Nevertheless, our review of the results showed that 77 of the 80 participants performed all steps successfully. A total of three use errors were committed on essential steps by three moderator-trained participants (2 patients and 1 caregiver):

- One moderator-trained patient and one moderator-trained caregiver participant lost the medication prior to administration as a result of the plunger rod pushing down on the tabletop during cap removal. This action resulted in a stream of medication onto the table and surrounding area.
- One moderator-trained, injection-naïve participant failed to push the plunger upon needle insertion. The participant indicated that he/she expected that the syringe would inject the medication on its own. Additionally, the participant stated the he/she did not know that they had access to the IFU for the simulated injection and stated that they would have used the instructions

at home. The participant self-detected the use error during the root cause interview and then went on to demonstrate a successful injection.

Our evaluation of these errors indicated that they are associated with first time use of injectable products administered via PFS and may not recur, as shown in the study that the users would detect and correct the error immediately. We further evaluated the risks associated with the use of the product and did not identify any new or unique risks compared to currently marketed prefilled syringes for this patient population and for this indication. As such, we do not have any recommendations to further mitigate the errors.

In addition, we noted multiple use-errors on non-essential tasks (e.g. checking expiration date, inspection the drug appearance, inspection for damage, clean injection site, washing hands). See Appendix C for more details. We do not have any recommendations to address the use errors at this time.

Regarding the proposed label and labeling, we note the following deficiencies:

- The presentation of the strength statement can be improved to increase readability. As currently presented there is no space between the numbers and the unit of measure (i.e. proposed 210mg/1.5mL vs. recommended 210 mg/1.5 mL).
- The ^{(b) (4)} on the container label interfers with the legibility of information.
- The strength statement, as presented within the orange circle on the carton labeling, does not include the total volume (i.e. proposed 210 mg vs. recommended 210 mg/1.5 mL) in accordance with USP General Chapter <1>.
- The carton labeling include two statements related to dosing: (b) (4) (b) (4)

^{(b) (4)}. Including two different statements related to dosing

may be confusing for end users.

4 CONCLUSION & RECOMMENDATIONS

We find the HF validation study results acceptable. We identified areas for improvement with regards to the visual display of the strength on the container labels and carton labeling of the proposed product. Additionally, we identified other aspects of the labels and labeling that should be revised to improve readability of important information and promote the safe use of the product. We provide letter-ready recommendations for Valeant Pharmaceuticals Luxembourg S.a.r.l. in Section 4.1 below, to be implemented prior to approval of BLA 761032.

4.1 RECOMMENDATIONS FOR VALEANT PHARMACEUTICALS LUXEMOURG S.a.r.l.

- A. General Comments (All container labels and carton labeling)
 - 1. Revise the strength statement to include a space between the number and the unit of measure (i.e. 210 mg/1.5 mL) to improve legibility.
- B. Container Label
 - 1. Delete ^{(b) (4)} to prevent clutter and improve legibility on these small labels.
- C. Carton Labeling (sample and trade)
 - 1. Revise the strength statement presented within the orange circle to include the total volume (i.e. 210 mg/1.5 mL) in accordance with USP Chapter <1>.
 - 2. On the principal display panels (top and side panels with the orange box), re-locate the statement within the orange box that reads "See package insert for ^{(b) (4)} and instructions for

use" to the top of the box and revise to read "See package insert for dosing information and Instructions for Use".

- 3. On the principal display panel (top panel), delete the statement " (b) (4)
 " as users are referred to the package insert and instructions for use in other sections of the carton labeling.
- D. Carton Labeling (sample)
 - 1. On the principal display panels (top and side panels with the orange box), relocate the route of administration statement to appear below the strength statement (where the sample statement is currently presented).
 - 2. In order to implement recommendation D.1., relocate the sample statement to the location where the route of administration statement is currently presented.
- E. Carton Labeling (trade)
 - 1. On the principal display panel (side panel with the orange box), relocate the route of administration statement to appear below the strength statement.

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Siliq that Valeant Pharmaceuticals Luxembourg S.a.r.l. submitted on August 12, 2016.

Table 2. Relevant Product Information for Siliq				
Initial Approval Date	N/A			
Active Ingredient	Brodalumab			
Indication	Treatment of moderate to severe plaque psoriasis in adult patients who are candidates for systemic therapy or phototherapy			
Route of Administration	Subcutaneous			
Dosage Form	Injection			
Strength	210 mg/1.5 mL			
Dose and Frequency	210 mg by subcutaneous injection at Weeks 0, 1, and 2 followed by 210 mg every 2 weeks			
How Supplied	Sample: Carton of 1- 210 mg/1.5 mL PFS Trade: Carton of 2- 210 mg/1.5 mL PFS			
Storage	Refrigerated at 2°C to 8°C (36°F to 46°F)			
Container Closure	2.25 mL glass (Type 1) syringe with a staked in place stainless steel needle			

APPENDIX B. PREVIOUS DMEPA REVIEWS

B.1 Methods

On Septemebr 15, 2016 we searched the L:drive using the term, Siliq and brodalumab, to identify reviews previously performed by DMEPA.

B.2 Results

Our search did not identified any previous relevant review.

APPENDIX C. PREFILLED SYRINGE HUMAN FACTORS STUDY RESULTS

Objectives

The first objective of this study was to validate, through objective and subjective evidence, that participants representative of the intended user population can safely demonstrate proficiency with the following essential steps:

Remove the prefilled syringe from packaging

Remove needle shield by pulling straight off

Place injection needle on recommended injection site surface and pierce the skin (simulation with skin pad)

Depress the syringe plunger rod to empty the entire drug product

Remove device from injection site without needle-stick injury

Dispose of device without needle-stick injury

The second objective of this study was to assess performance of these tasks under learning decay conditions.

Intended User Population, Intended Use and Use Environments

The Siliq PFS intended user population includes HCPs, caregivers, and patients. The Siliq PFS is a singleuse, disposable device intended to administer a fixed dose of brodalumab drug product into the subcutaneous tissue (abdomen, thigh, or outer area of upper arm) of patients for the treatment of Plaque Psoriasis and Psoriatic Arthritis. It is intended for use by patients and caregivers in a non-healthcare environment or by HCPs in a clinical setting.

Device Configuration

Siliq PFS will be commercially available in 1.5 mL fill volume for a 210 mg dose.

Packaging Configurations

This study evaluated the two-pack packaging configuration for Siliq PFS. The larger package (two-pack) was used for this study because it was considered the most challenging usage scenario; specifically, users had to first determine the correct number of syringes to use for the simulated drug administration.

Participant Demographics

The study sample consisted of 80 participants from three user groups: 1) Patients (n=32), 2) Caregivers (n=32) and 3) HCPs (n=16). See Table 10 for participant demographic information.

Table 10: Demographics - 1.5 mL Fill PFS with Standard IFU

Demographics	Recruited Participan	ts		
	Patients (n=32) - 49 years old (range: 21-70)			
A	Caregivers (n=32) - 44 years old (range: 24-65)			
Average Age	HCP (n=16) - 48 years old (ran	ige: 32-63)		
	Total (n=80) - 47 years old (ra	nge: 21-70)		
Gender	56 Female, 24 Male	2		
	Patients - 19 naïve, 13 expe	erienced		
Injection Experience (Patients and Caregivers Only)	Caregivers - 14 naïve, 18 exp	perienced		
	Total - 33 naïve, 31 exper	ienced		
Average HCP Experience (HCPs Only)	19 years as HCP (range: 4-40)			
	Level Frequency			
	Moderate	7		
Hand Dysfunction (Patients Only)	Minor	2		
	None	23		
	Level Frequency			
	High School	4		
	Some College	21		
Education	Associates	10		
	Bachelors	32		
	Graduate Degree	13		

Learning Decay (Loss of Information Retention) Evaluation

To evaluate the effects of learning decay, moderatortrained participants were provided a 60-minute break between the training and testing portions of the study.

Test Conditions

Moderator-trained: Approximately half of the patient participants and approximately half of the caregiver participants were trained on how to use the PFS by the moderator following a training walk-through script covering key points from the IFU. After training, participants were given a 60-minute break, and then returned to the study room to prepare and administer a complete dose (simulated) using a Siliq PFS with Flange Extender Two-Pack Box.

Self-trained: Approximately half of patient participants and approximately half of the caregiver participants were self-trained using the assigned IFU. Participants prepared and administered a complete dose (simulated) using a Siliq PFS with Flange Extender Two-Pack Box

Results

Key Results

According to the Siliq PFS Summative Study Protocol, essential steps were defined as the tasks necessary for successful use of the device for its intended purpose. For the Siliq PFS system, this includes the tasks necessary to enable the patient to receive a complete dose.

A total of 77 out of 80 participants (96%) that used the standard IFU with the 1.5 mL fill PFS successfully completed the tasks necessary to administer a complete dose.

Table 11 below lists each essential step and the corresponding performance rate by distinct user group (i.e., patient, caregiver, and HCP) and training condition (i.e., moderator-trained vs. self-trained). Performance rate is defined as the percentage of participants that completed a given step without committing a use error during the study.

Performance was nearly the same with the 1.5 mL fill PFS with standard IFU for training conditions and user groups with respect to essential steps; a total of 3 out of 32 moderator trained participants committed 3 essential step use errors (2 by patients and 1 by a caregiver), while 0 out of 48 self-trained participants committed 0 essential step use errors.

Essential Stens	Moderator-Trained (n=32)		Self-Trained (n=48)		
Lasennal Steps	Patient	Caregiver	Patient	Caregiver	HCP
	(n=16)	(n=16)	(n=16)	(n=16)	(n=16)
Remove device from packaging	100%	100 %	100 %	100 %	100 %
	16 / 16	16 / 16	16 / 16	16 / 16	16 / 16
Remove needle cover	94 %	94 %	100 %	100 %	100 %
	15 / 16	15 / 16	16 / 16	16 / 16	16 / 16
Place injection needle on injection site surface and pierce the skin	100%	100 %	100 %	100 %	100 %
	16 / 16	16 / 16	16 / 16	16 / 16	16 / 16
Depress the syringe plunger rod to	94 %	100 %	100 %	100 %	100 %
empty the entire drug product	15 / 16	16 / 16	16 / 16	16 / 16	16 / 16
Remove device from injection site without needle-stick injury	100%	100 %	100 %	100 %	100 %
	16 / 16	16 / 16	16 / 16	16 / 16	16 / 16
Dispose of device without needle stick injury	100%	100 %	100 %	100 %	100 %
	16 / 16	16 / 16	16 / 16	16 / 16	16 / 16

Table 13 shows there were a total of 3 essential step use errors committed by 3 participants.

Table 13: Number of Essential Step Use Errors

Essential Stens	Moderator-Trained (n=32)		Self-Trained (n=48)		
	Patient (n=16)	Caregiver (n=16)	Patient (n=16)	Caregiver (n=16)	HCP (n=16)
Remove device from packaging	0	0	0	0	0
Remove needle cover	1	1	0	0	0
Place injection needle on injection site surface and pierce the skin	0	0	0	0	0
Depress the syringe plunger rod to empty the entire drug product	1	0	0	0	0
Remove device from injection site without needle-stick injury	0	0	0	0	0
Dispose of device without needle stick injury	0	0	0	0	0
Total	2	1	0	0	0

According to the Siliq PFS Summative Study Protocol, safety critical use errors were defined as hazards/failures identified in the uRA with a severity of 5 or higher.

A total of 69 use errors with a severity of 5 or higher were committed by 49 out of the 80 participants. Note that 34 of these 69 use errors (49%) were failures to check the expiry date.

Table 12 below lists each IFU step associated with a use error with a severity of 5 or higher and the corresponding performance rate by distinct user group and training condition. Performance rate is defined as the percentage of participants that completed a given step without committing a use error during the study.

Performance was nearly the same for training conditions and user groups with respect to these use errors, for the exception of HCPs, who on average committed slightly fewer of these use errors than patients and caregivers; a total of 21 out 32 moderator-trained participants (10 patients, 11 caregivers) committed 27 of these 69 use errors, while 28 out of 48 self-trained participants (11 patients, 10 caregivers, 7 HCPs) committed the remaining 42 use errors.

Table 12: Performance Rate for IFU Steps Associated with Use Errors with a Severity of 5 or Higher for 1.5 mL Fill PFS with Standard IFU

IFU Steps Associated	Moderator-Trained (n=32)		Self-Trained (n=48)		
Severity of 5 or Higher	Patient	Caregiver	Patient	Caregiver	HCP
	(n=16)	(n=16)	(n=16)	(n=16)	(n=16)
Inspect drug appearance	100%	81 %	94%	100 %	88 %
	16 / 16	13 / 16	15 / 16	16 / 16	14 / 16
Inspect for damage	88 %	88 %	94 %	94 %	94 %
	14 / 16	14 / 16	15 / 16	15 / 16	15 / 16
Check expiration date	63 %	56%	63 %	44%	63 %
	10 / 16	9 / 16	10 / 16	7 / 16	10 / 16
Wash hands	69 %	75 %	88 %	100 %	94 %
	11 / 16	12 / 16	14 / 16	16 / 16	15 / 16
Clean site with alcohol wipe	94%	88 %	69 %	88 %	100 %
	15 / 16	14 / 16	11 / 16	14 / 16	16 / 16

Table 14 shows there were a total of 69 use errors committed by 49 participants.

Table 14: Number of IFU Step Use Errors with a Severity of 5 or Higher for 1.5 mL Fill PFS with Standard IFU

IFU Steps Associated	Moderator-Trained		Self-Trained		
with Use Errors with a Severity of 5 or Higher	Patient (n=16)	Caregiver (n=16)	Patient (n=16)	Caregiver (n=16)	HCP (n=16)
Inspect drug appearance	0	3	1	0	2
Inspect for damage	2	2	1	1	1
Check expiration date	6	7	6	9	6
Wash hands	5	4	2	0	1
Clean site with alcohol wipe	1	2	5	2	0
Total	14	18	15	12	10

Summary Conclusions 1.5 mL Fill PFS with Standard IFU

- A total of 77 out of 80 participants (96%) that used the standard IFU with the 1.5 mL fill PFS successfully completed the tasks necessary to administer a complete dose.
- Performance was nearly the same for training conditions and user groups with respect to essential steps.
- Performance was nearly the same for training conditions and user groups with respect to
 use errors with a severity of 5 or higher, for the exception of HCPs who on average
 committed slightly fewer of these use errors than patients and caregivers.

APPENDIX D. ISMP NEWSLETTERS

N/A

APPENDIX E. FDA ADVERSE EVENT REPORTING SYSTEM (FAERS) N/A

APPENDIX F. OTHER

APPENDIX G. LABELS AND LABELING

G.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,¹ along with postmarket medication error data, we reviewed the following Siliq labels and labeling submitted by Valeant Luxembourg on June 17, 2016.

- Container label
- Carton labeling
- Prescribing Information (not pictured)
- Instructions for Use (not pictured)

G.2 Label and Labeling Images (not to scale)

Prefilled Syringe Container Labels

(b) (4)

¹ Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

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CARLOS M MENA-GRILLASCA 10/04/2016

MISHALE P MISTRY 10/06/2016

QUYNHNHU T NGUYEN 10/06/2016

Clinical Inspection Summary

Date	August 24, 2016				
From	Roy Blay, Ph.D., Reviewer, GCPAB\OSI				
	Janice K. Pohlman, M.D., M.P.H., Team Leader, GCPAB\OSI				
	Susan D. Thompson, M.D., acting Branch Chief for				
	Kassa Ayalew, M.D., M.P.H., Branch Chief, GCPAB\OSI				
То	DDDP\Team Leader\David Kettl				
	DDDP\Medical Officer\Gary Chiang				
	DDDP\Project Manager\Strother Dixon				
NDA/BLA #	BLA 761032				
Applicant	AstraZeneca Pharmaceuticals LP				
Drug	Brodalumab (AMG 827)				
NME (Yes/No)	Yes				
Therapeutic Classification	Standard Review				
Proposed Indication(s)	Treatment of moderate to severe plaque psoriasis.				
Consultation Request Date	December 21, 2015				
Summary Goal Date	August 26, 2016				
Action Goal Date	November 2, 2016				
PDUFA Date	November 16, 2016				

1. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

The clinical sites of Drs. Elzakowska-Bober, Lebwohl, and Toth were inspected in support of this BLA, and the final classification of these inspections was No Action Indicated (NAI).

Based on the results of the clinical investigator inspections, the studies appear to have been conducted adequately, and the data generated by these sites appear acceptable in support of the respective indication.

2. BACKGROUND

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

Protocol 20120102, entitled "A Phase 3 Study to Evaluate the Efficacy, Safety, and Effect of Withdrawal and Retreatment With Brodalumab in Subjects With Moderate to Severe Plaque Psoriasis: AMAGINE-1" and identical protocols 20120103 and 20120104, entitled, "A Phase 3 Study to Evaluate the Efficacy and Safety of Induction and Maintenance Regimens of Brodalumab Compared With Placebo and Ustekinumab in Subjects With Moderate to Severe Plaque Psoriasis: AMAGINE-2", and, "A Phase 3 Study to Evaluate the Efficacy and Safety of Induction and Maintenance Regimens of Brodalumab Compared With Placebo and Ustekinumab in Subjects With Moderate to Severe Plaque Psoriasis: AMAGINE-3", respectively, were inspected in support of this application.

Protocol 20120102

This study was conducted with 661 randomized subjects at 73 centers in Europe, Canada, and the United States.

This double-blind, placebo-controlled study randomized subjects to evaluate brodalumab (210 mg every 2 weeks [Q2W] and 140 mg Q2W) versus placebo in a 1:1:1 ratio during the induction phase (12 weeks). At Week 12, based on the static physician's global assessment, subjects were re-randomized in a 1:1 ratio to either placebo or to continue brodalumab at their induction dose for long-term evaluation.

The co-primary endpoints for this study compared PASI 75 and sPGA success (clear [0] or almost clear [1]) at Week 12 between the two brodalumab treatment arms with placebo. The primary study objectives of this study compared to placebo were to:

- evaluate the efficacy of brodalumab (210 mg Q2W and 140 mg Q2W) in subjects with moderate to severe plaque psoriasis, as measured by the proportion of subjects who achieved success (clear [0] or almost clear [1]) on the static physician's global assessment (sPGA) at week 12.
- evaluate the efficacy of brodalumab (210 mg Q2W and 140 mg Q2W) in subjects with moderate to severe plaque psoriasis, as measured by the proportion of subjects who achieved 75% improvement in Psoriasis Area and Severity Index (PASI; PASI 75) at week 12.

Protocol 20120103

This study was conducted at 142 centers in Australia, Austria, Canada, Czech Republic, France, Hungary, Netherlands, Poland, Portugal, Spain, and the U.S.

This was a double-blind, double-dummy, Phase 3 study to evaluate the efficacy and safety of induction and maintenance regimens of brodalumab compared with placebo and ustekinumab in subjects with moderate to severe plaque psoriasis. After screening, subjects entered a 12-week, randomized, double-blind, placebo- and active-controlled phase (induction phase) during which they received subcutaneous (SC) injections of brodalumab (or placebo to match brodalumab) and SC injections of ustekinumab (or placebo to match ustekinumab). Subjects were re-randomized at Week 12 when they entered the maintenance phase. At Week 52, subjects could continue on the study in the long-term extension phase.

Within the placebo groups, the co-primary endpoints were PASI 75 (210 mg Q2W vs placebo and 140 mg Q2W vs placebo) and sPGA success (210 mg Q2W vs placebo and 140 mg Q2W vs placebo) at Week 12. Within the ustekinumab family, the primary endpoint was PASI 100 (210 mg Q2W vs ustekinumab and weight-based brodalumab [140 mg for subjects \leq 100 kg and 210 mg for subjects > 100 kg] vs ustekinumab) at Week 12.

The primary study objectives compared to placebo were to:

- evaluate the efficacy of brodalumab (210 mg every 2 weeks [Q2W] and 140 mg Q2W) in subjects with moderate to severe plaque psoriasis, as measured by the proportion of subjects achieving 75% improvement in Psoriasis Area and Severity Index (PASI; PASI 75) at Week 12
- evaluate the efficacy of brodalumab (210 mg Q2W and 140 mg Q2W) in subjects with moderate to severe plaque psoriasis, as measured by the proportion of subjects achieving success (clear [0] or almost clear [1]) on the static Physician's Global Assessment (sPGA) at Week 12

The primary study objective was to compare the efficacy of ustekinumab to the efficacy of brodalumab (210 mg Q2W and 140 mg Q2W for subjects \leq 100 kg and 210 mg Q2W for subjects > 100 kg) in clearing psoriasis in subjects with moderate to severe plaque psoriasis, as measured by the proportion of subjects achieving PASI 100 at week 12.

Protocol 20120104

This study was conducted at 142 centers in Australia, Canada, Europe, and the United States.

The primary study objectives and efficacy endpoints were identical to that of Protocol 20120103.

Dr. Elzakowska-Bober's site was selected because it was the highest enrolling site for Study 04.

Dr. Lebwohl's site was selected because it had the only death by suicide. The site also had a low number of ustekinumab responders.

Dr. Toth's site was selected because all subjects at the 210 mg brodalumab dose responded while none of the subjects on placebo responded.

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

Site #/ Name of CI/ Address	Protocol #/ # of Subjects (enrolled)	Inspection Dates	Classification
1-57XSCV_48003 Elzakowska-Bober, Anna Aleja Lotnikow Polskich 82 Swidnik, 21-040 Poland	20120104/ 68	18-22 Apr 2016	NAI
1-6F5F9V_66026 Lebwohl, Mark 5 East 98 Street New York, NY 10029	20120103/ 49	11-16 Feb 2016	NAI
1-433ULZ_16007 Toth, Darryl 2425 Tecumseh Road East, Suite 210 Windsor, ON N8W 1E6 Canada	20120102/ 25	11-14 Apr 2016	NAI

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. Anna Elzakowska-Bober, M.D.

At this site for Protocol 20120104, 96 subjects were screened, 68 subjects were enrolled, and 65 subjects completed the study.

Study records were reviewed for all 67 subjects reaching the primary efficacy endpoint at Week 12 (PASI and sPGA scores). The source documents were compared with the information contained in the line listings. Review of the records included, but was not limited to, training logs, IRB correspondence and approvals, financial disclosure, IRB, sponsor and monitoring correspondence, inclusion/exclusion criteria, randomization, electronic Case Report Forms (eCRFs), adverse events, concomitant medications, test article accountability and storage.

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. Mark Lebwohl , M.D.

At this site for Protocol 20120103, 57 subjects were screened and 49 subjects were enrolled. None of the subjects completed the study because the study was terminated in June of 2015 by the original sponsor, Amgen. The protocol specified that assessments of the primary and secondary efficacy endpoints occur at Week 12. Because the study continued and was subsequently terminated during its maintenance study phase, these endpoints were able to be verified.

Source data on paper records were transcribed to a sponsor-provided, web-based electronic data capture program (Medidata Rave). Source data was compared to line listings. The records of 20 subjects were reviewed. Records reviewed included, but were not limited to, monitoring reports, financial disclosure, randomization, stratification, primary and secondary efficacy endpoints, adverse events, concomitant medications, and test article accountability.

Signed informed consent was obtained from all 49 enrolled subjects prior to study entry. Numerous discrepancies were noted between the subject source records, the electronic Case Report Forms (eCRFs), and the line listings. In all cases, source records matched the eCRFs but multiple adverse events were not included in the line listings reported to the BLA. The clinical study report submitted to the BLA had a data cut-off date of September 22, 2014 and all but two adverse events not included in the line listing occurred after the data cut-off date. The sponsor has since submitted an updated report of adverse events in the Integrated Summary of Safety submitted as part of the four month BLA safety update. The adverse events in the EIR noted to be absent from the existing line listings including an SAE of suicide were documented in the updated adverse event listing.

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

3. Darryl Toth, M.D.

At this site for Protocol 20120102, 27 subjects were screened and 25 subjects were enrolled. No subjects completed the study due to termination of the study by the sponsor in June 2015; however, all 25 enrolled subjects completed the initial 12 weeks of the study at which time the efficacy endpoints were assessed.

The records of 22 subjects were reviewed. Records reviewed included, but were not limited to, financial disclosure, IVRS reports, laboratory results, protocol deviations, dosing records, concomitant medications, monitoring logs, IRB correspondence, and drug accountability and storage

Signed informed consent was obtained from all screened subjects prior to study entry. None of the subjects completed the study because the study was terminated in June of 2015 by the original sponsor, Amgen. The program was then transitioned to the current sponsor, AstraZeneca Pharmaceuticals LP.

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

Janice Pohlman, M.D., M.P.H. Team Leader Good Clinical Practice Assessment Branch Division of Clinical Compliance Evaluation Office of Scientific Investigations

CONCURRENCE:

{See appended electronic signature page}

Susan D. Thompson, M.D., for 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 761032 DDDP\Division Director\Kendall Marcus DDDP\Team Leader\David Kettl DDDP\Medical Officer\Gary Chiang DDDP\Project Manager\Strother Dixon OSI\DCCE\Division Director\Ni Khin OSI\ DCCE\GCPAB\Branch Chief\Kassa Ayalew OSI\ DCCE\GCPAB\Team Leader\Janice Pohlman 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 08/24/2016

JANICE K POHLMAN 08/24/2016

SUSAN D THOMPSON 08/24/2016



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

Pregnancy and Lactation Labeling Rule (PLLR) Labeling Review

Date:	August 3, 2016	Date Consulted: December 1, 2015
From:	Christos Mastroyannis, M.D., Medical Officer, Maternal Health Division of Pediatric and Maternal Health (DPMH)	
Through:	Tamara Johnson, M.D., M.S., Team Leader, Maternal Health Division of Pediatric and Maternal Health	
	Lynne P. Yao, M.D., Divisio Division of Pediatric and Ma	n Director, ternal Health
То:	Division of Dermatology and Dental Products (DDDP)	
Drug:	Siliq (brodalumab) injection	
BLA:	761032	
Subject:	Pregnancy and Lactation Labeling	
Proposed Indication:	The treatment of adult patients with moderate-to-severe plaque psoriasis who are candidates for systemic therapy or phototherapy	
Applicant:	AstraZeneca UK	
Materials Reviewed:	 Applicant's proposed November 16, 2015, December 1, 2015, D labeling review July 12, 2016, Pharm D. Booker, Ph.D. 	labeling Applicants submission DDP's request to DPMH-MHT for acology/Toxicology review by Carmen
Consult Question:	Assist with Pregnancy and Lactation Labeling	

REGULATORY HISTORY

The applicant submitted an original 351 (a) biologic license application (BLA) for Siliq (brodalumab) injection, BLA 761032, on November 16, 2015. The proposed indication is for the treatment of adults with moderate to severe plaque psoriasis who are candidates for systemic therapy or phototherapy. No other indications exist. The Division of Dermatology and Dental Products (DDDP) consulted the Division of Pediatric and Maternal Health (DPMH) on December 1, 2015, to assist with reviewing the Pregnancy and Lactation subsections of labeling.

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

BACKGROUND

Drug Characteristics

Siliq (brodalumab) is a monoclonal (mAB) IgG2 antibody that binds with high affinity to human IL-17 receptor A (IL-17RA) and blocks the activity of IL-17A, IL-17F, IL-17A/F heterodimer, and IL-25. Other drugs in the IL-17A antagonist drug class include:

- Taltz (ixekizumab)
- Cosentys (secukinumab)

Other mAB treatments for psoriasis include:

- Stelara (ustekinumab) is an IgG 1K, anti-IL 12 and 23
- Remicade (infliximab) is a chimeric IgG 1K anti-TNF
- Humira (adalimumab) is an IgG 1 anti-TNF

IL-17RA is found on a variety of cells including fibroblasts, epithelial cells and monocytes. IL-25 is associated with Th2-type inflammatory processes and is produced by epithelial cells, Th2 cells, eosinophils, and basophils. IL-17A, IL-17F and IL-17A/F are produced by Th cells and innate immune cells. These cytokines also induce pro-inflammatory mediators from epithelial cells and fibroblasts that promote tissue inflammation and destruction as well as the maturation of neutrophils and dendritic cells.

Brodalumab has a molecular weight of 144,000 Daltons, a half-life of 10.9 days, and bioavailability of 54.7%. Brodalumab may increase the risk of infections.

Disease Background

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.^{1,3}

³ Zip C: A practical guide to dermatological drug use in pregnancy. Skin therapy letter 2006;11(4)1-4 Reference ID: 3971145

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 Jul 7. [Epub ahead of print]

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*,"⁴ also known as the Pregnancy and Lactation Labeling Rule (PLLR) went into effect. 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 create a new subsection for information with regard to females and males of reproductive potential. Specifically, the pregnancy categories (A, B, C, D and X) are removed from all prescription drug and biological product labeling and a new format is required for all products that are subject to the 2006 Physicians Labeling Rule⁵ format to include information about the risks and benefits of using these products during pregnancy and lactation.

REVIEW

Pregnancy

Nonclinical experience

A combined embryofetal development and pre- and post-natal development study was conducted in cynomolgus monkeys administered brodalumab. No brodalumab-related effects on embryo-fetal toxicity or malformations or on morphological, functional or immunological development were observed in infants from pregnant monkeys administered weekly subcutaneously doses of brodalumab up to 26 times the maximum recommended human dose (MRHD) from the beginning of organogenesis to parturition (on a mg/kg basis of 90 mg/kg/week). MRHD is 3.5 mg/kg (210 mg \div 60 kg = 3.5 mg/kg). The reader is referred to the Pharmacology/Toxicology review⁶ by Carmen D. Booker, Ph.D. for further details.

Review of Literature

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

Review of Clinical Trials

Because the drug has not yet been approved, no pharmacovigilance database has been established. Across the brodalumab clinical program, 34 pregnancies (see Table 1 for pregnancy outcomes) following maternal brodalumab exposure and 40 pregnancies following paternal brodalumab exposure have been reported across all brodalumab clinical studies. These limited clinical data are insufficient to draw meaningful safety conclusions about the effects of brodalumab during pregnancy and lactation.

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

⁵ Requirements on Content and Format of Labeling for Human Prescription Drug and Biological Products, published in the Federal Register (71 FR 3922; January 24, 2006).

⁶ Pharmacology/Toxicology Review. Siliq (brodalumab) injection Carmen D. Booker, Ph.D, July 12, 2016 DARRTS Reference ID 3957348

Birth Outcomes	Maternal Exposures (n=34)
Full term birth without complications	8
Normal live birth	2
Full term birth with complications	0
Spontaneous abortion NOS	5
Ectopic pregnancy	2
Elect Term Family Planning	4
Elective Term NOS	3
Unknown	8
Lost to follow up	2
Unknown Lost to follow up	8 2

Table 1: Cumulative birth outcomes for maternal exposure pregnancies to brodalumab in the clinical program through 22 September 20147

Abbreviations: NOS not otherwise specified.

Summary

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

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

Lactation

Nonclinical Experience

In cynomolgus monkeys administered brodalumab at 90 mg/kg weekly throughout pregnancy, brodalumab was detected in milk up to 14 days after birth at concentrations that were approximately 1000 fold lower than those measured in maternal serum.⁸

Review of Literature

DPMH conducted a search of Medications and Mother's Milk⁹, the Drugs and Lactation Database (LactMed)¹⁰, Micromedex¹¹, and of published literature in PubMed using the search terms "brodalumab and lactation" and "brodalumab and breastfeeding." No reports of clinical lactation studies or case reports

⁷ AstraZeneca UK submission, Section 2.7.4, Summary of Clinical Safety, p:219, November 16, 2015

¹¹ Truven Health Analytics information, http://www.micromedexsolutions.com/. Reference ID: 3971145

⁸ Applicant's proposed labeling

⁹ Hale, Thomas (2012) Medications and Mothers' Milk. Amarillo, Texas Hale Publishing

¹⁰ http://toxnet.nlm.nih.gov/cgi-bin/sis/htmlgen?LACT. The LactMed database is a National Library of Medicine (NLM) database with information on drugs and lactation geared toward healthcare practitioners and nursing women. The LactMed database provides information when available on maternal levels in breast milk, infant blood levels, any potential effects in the breastfed infants if known, alternative drugs that can be considered and the American Academy of Pediatrics category indicating the level of compatibility of the drug with breastfeeding.

of brodalumab use in lactating women were found in published literature.

A recent published review article about other TNF α inhibitors (infliximab and adalimumab) in pregnancy and lactation states that concentrations of infliximab and adalimumab in breast milk are significantly lower than maternal serum levels, however, "a deleterious effect of this exposure on the neonate, although unlikely, cannot be excluded."¹² Three patients who received infliximab during and after pregnancy were followed prospectively. The patients received infliximab (5 mg/kg) at regular intervals until approximately gestational week 30, and resumed infliximab within 3 to 14 days after delivery. The drug was detected in the mothers' sera, but not in their breast milk or in the sera of the newborns. Data from this small series of patients suggest that infliximab was not transferred from mother to child, either in utero or through breast milk. The authors concluded that mothers receiving infliximab should not be discouraged from breastfeeding their children (at least if they have abstained from infusions after week 32 of pregnancy). In these studies where infliximab (or adalimumab) was not detected in breast milk, the researchers used a commercial kit standardized according to blood levels. In contrast, other researchers who used control breast milk samples for calibration of the standard curve recorded detectable levels of infliximab or adalimumab in breast milk, although in concentrations that were significantly lower than in serum; nevertheless, miniscule amounts of these anti-TNF drugs were detected in the milks tested^{15,16}. Serum and breast milk were obtained after delivery from three patients with Crohn's disease, infliximab levels in breast milk rose to 101 ng/ml within 2–3 days of the infusion; this level was roughly 1/200th of the level in blood. These findings were recently confirmed by Fritzsche et al., who prospectively followed breastfed children under maternal treatment with infliximab or adalimumab.¹⁷ The concentration range of infliximab in the breast milk of two patients was similar to the levels measured by Ben-Horin et al., peaking at ~100 ng/ml.¹⁵

The miniscule amounts of infliximab/adalimumab transferred in breast milk are unlikely to result in systemic immune suppression in the infant; in addition, this small quantity most probably undergoes proteolysis in the stomach and intestine after ingestion. Nevertheless, local effects of exposure on the neonates' intestine cannot be excluded and merit further investigation.¹³,¹⁴,¹⁵

Summary

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

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

Females and Males of Reproductive Potential

Nonclinical Experience

Animal fertility studies did not demonstrate any effects on fertility at AUC exposure levels up to 50-fold higher than in subject receiving brodalumab at 210mg every two weeks.

¹² Gisbert JP, Chaparro M. Safety of anti-TNF agents during pregnancy and breastfeeding in women with inflammatory bowel disease. Am J Gastroenterol. 2013;108:1426-38.

¹³ Ben-Horin S, Yavzori M, Kopylov U et al. Detection of infliximab in breast milk of nursing mothers with inflammatory bowel disease. J Crohns Colitis 2011;5:555–558.

¹⁴ Ben-Horin S, Yavzori M, Katz L et al. Adalimumab level in breast milk of a nursing mother. Clin Gastroenterol Hepatol 2010;8:475–476

¹⁵ Fritzsche J, Pilch A, Mury D et al. Infliximab and adalimumab use during breastfeeding. J Clin Gastroenterol 2012;46:718–

Review of Literature

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

Summary

Animal reproductive studies of administration of brodalumab did not show any adverse effects on fertility. Since there are no human data available on the effect of brodalumab on fertility, Section 8.3, Females and Males of Reproductive Potential, will not be included in Siliq labeling.

CONCLUSION

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

- Pregnancy, Section 8.1
 - The "Pregnancy" section of Siliq labeling was formatted in the PLLR format to include: "Pregnancy Exposure Registry," "Risk Summary," and "Data" sections.
- Lactation, Section 8.2
 - The "Lactation" section of Siliq labeling was formatted in the PLLR format to include the "Risk Summary" section.
- Patient Counseling Information, Section 17
 - The "Patient Counseling Information" section of labeling was updated to correspond with changes made to sections 8.1 and 8.20f labeling.

RECOMMENDATIONS

- 1.) DPMH participated in a labeling meeting with DDDP. DPMH revised sections 8.1, 8.2, and 17 of Siliq labeling for compliance with the PLLR. DPMH refers to the final NDA action for final labeling. DPMH proposed labeling for Siliq is included in Appendix A.
- 2.) DPMH proposes a Post-Marketing Requirement that requires the applicant to perform a pregnancy exposure registry study and a complementary study to assess the safety of Siliq in pregnant women. The language for the PMR is included in Appendix B.

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.¹⁶ In addition, pregnancy registries allow collection of patient level detailed data on 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.¹⁷ 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.

¹⁶ FDA Guidance for Industry Establishing Pregnancy Exposure Registries

¹⁷ 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

APPENDIX A: DPMH PROPOSED PREGNANCY AND LACTATION LABELING EDITS FOR SILIQ

FULL PRESCRIBING INFORMATION

8 USE IN SPECIFIC POPULATIONS 8.1 Pregnancy

(b) (4)

Risk Summary

There are no human data on SILIQ use in pregnant women to inform a drug- associated risk. Human IgG antibodies are known to cross the placental barrier; therefore, SILIQ may be transmitted from the mother to the developing fetus. In a combined embryofetal development and pre- and post-natal development study, no adverse developmental effects were observed in infants born to pregnant monkeys after subcutaneous administration of brodalumab during organogenesis through parturition at doses up to 26-times the maximum recommended human dose (MRHD)[*see Data*].

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

A combined embryofetal development and pre- and post-natal development study was conducted in cynomolgus monkeys administered brodalumab. No brodalumab-related effects on embryofetal toxicity or malformations, or on morphological, functional or immunological development were observed in infants from pregnant monkeys administered weekly subcutaneous doses of brodalumab up to 26 times the MRHD from the beginning of organogenesis to parturition (on a mg/kg basis of 90 mg/kg/week).

8.2 Lactation

Risk Summary

There are no data on the presence of brodalumab in human milk, the effects on the breastfed infant, or the effects on milk production. Brodalumab was detected in the milk of lactating cynomolgus monkeys.

The

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

17 PATIENT COUNSELING INFORMATION

APPENDIX B: DPMH PMR LANGUAGE FOR SILIQ PREGNANCY EXPOSURE REGISTRY

DPMH recommends the following PMR language:

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

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

And

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

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

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

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CHRISTOS MASTROYANNIS 08/11/2016

TAMARA N JOHNSON 08/11/2016

LYNNE P YAO 08/12/2016



DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration Office of the Commissioner Office of Good Clinical Practice & Office of Pediatric and Therapeutics 10903 New Hampshire Avenue Silver Spring, MD 20993-0002

MEMORANDUM

Date:	August 10, 2016
From:	Kevin Prohaska, D.O., M.P.H., Captain (USPHS) Office of Good Clinical Practice, Office of the Commissioner
	Robert "Skip" Nelson, M.D., Ph.D.
	Deputy Director and Senior Pediatric Ethicist
	Office of Pediatric Therapeutics, Office of the Commissioner
To:	Strother D. Dixon
	Senior Regulatory Project Manager
	Division of Dermatology and Dental Products, Center for Drug Evaluation and Research
Re:	BLA 761032 Siliq (brodalumab) injection, 210 mg/1.5 ml

I. Materials Reviewed

- Recordings of the FDA Dermatologic and Ophthalmic Drug Advisory Committee meeting held on July 19, 2016; available at <u>http://www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/DermatologicandOphthalmicDrugsAdvisoryCommittee/ucm506087.htm</u>
- 2) Dermatologic and Ophthalmic Drugs Advisory Committee Meeting Briefing Document, dated July 19, 2016.
- 3) Division of Psychiatry Products (DPP) consultative review, dated April 25, 2016
- 4) Division of Epidemiology I (DEP-I) consultative review, dated March 22, 2016.
- Valeant Pharmaceuticals document labeled "Food and Drug Administration Dermatologic and Ophthalmic Drug Advisory Committee", dated July 19, 2016.
- 6) Corrona Registry details, available at http://www.corrona.org/registries/psoriasis
- 7) Belmont Report, available at <u>http://www.hhs.gov/ohrp/regulations-and-policy/belmont-report/index.html#xrespect</u>.
- Council for International Organizations of Medical Sciences (CIOMS), "International Ethical Guidelines for Biomedical Research Involving Human Subjects": http://www.recerca.uab.es/ceeah/docs/CIOMS.pdf
- 9) Draft FDA Guidance "Format and Content of Proposed Risk Evaluation and Mitigation Strategies (REMS), REMS Assessments, and Proposed REMS Modifications", dated September 2009, available at <u>http://www.fda.gov/ucm/groups/fdagov-public/@fdagovdrugs-gen/documents/document/ucm184128.pdf</u>.

II. Background

On July 21, 2016 the Office of Good Clinical Practice (OGCP) and the Office of Pediatric Therapeutics (OPT) within the Office of the Commissioner received a consultative request from the Division of Dermatology and Dental Products (DDDP) in the Center for Drug Evaluations and Research (CDER). The purpose of the request is for an ethical consultation to address the following concerns related to BLA 761032:

"The applicant proposed participation in the Corrona registry [a pre-existing registry used by several other sponsors of systemic drugs for treatment of moderate to severe psoriasis] to assess risk for suicide ideation and behavior as part of post-marketing risk management. At the advisory committee meeting held 7/19/16, several SGEs recommended mandatory patient enrollment in the registry (as a condition of receipt of the product) to improve signal detection. Please provide your perspective on these two approaches--voluntary patient enrollment versus mandatory patient enrollment."

Psoriasis is a common autoimmune skin disorder affecting 2-3% of the U.S. population. Approximately 20% of those affected have moderate to severe psoriasis affected >5% of the body surface area. Moderate to severe psoriasis can be a disabling condition that has a substantial impact on patients' lives. Psoriasis is associated with an increased risk of psoriatic arthritis, lymphomas, cardiovascular disease, Crohn's disease, and a variety of psychiatric conditions including dysthymia, major depression, suicidality, substance abuse, and generalized anxiety. There is currently no cure for psoriasis.

Product	Class
Acitretin	Retinoid
Methotrexate	Folate Antagonist
Cyclosporine	Inhibits IL-2
Apremilast	Phosphodiesterase 4 inhibitor
Etanercept	TNFa-blocker
Infliximab	TNFa-blocker
Adalimumab	TNFa-blocker
Ustekinumab	Interleukin-12 and -23 antagonist
Secukinumab	Interleukin-17A antagonist
Ixekizumab	Interleukin-17A antagonist

Approved systemic treatments for psoriasis are outlined in the following table:

The following image depicts the site of action within the cytokine cascade for the various biologic drug products used to treat psoriasis:



Note that ixekizumab and secukinumab are IL-17A antibodies directed at IL-17 cytokines; whereas the mechanism of action for brodalumab is distinct in that it binds to IL-receptors rather than cytokines.

The following image depicts the 12-week efficacy results seen for the biologic drug products approved for the treatment of psoriasis compared to brodalumab (Siliq).



Cosentyx (secukinumab); Taltz (ixekizumab); Siliq (brodalumab)

A variety of topical treatments are also available; however, they are rarely used alone for patients with moderate to severe psoriasis. In addition, subjects with moderate to severe psoriasis may be treated with phototherapy in combination with a photosensitizer (Psoralen); however, this treatment regimen requires frequent office visits and is associated with an increased risk of squamous cell carcinoma of the skin.

III. Product Description

Brodalumab (Siliq) injection, 210 mg/1.5 ml is being developed for the treatment of adults with moderate to severe plaque psoriasis who are candidates for systemic therapy or phototherapy. Brodalumab is a human monoclonal antibody (IgG2) which binds to human interleukin-17 receptor A (IL-17RA) and blocks the biological activities of IL-17A, IL-17C, IL-17F, IL-17A/F heterodimer and IL-25. IL-17A is a naturally occurring cytokine that is involved in normal inflammatory and immune responses and plays a role in the pathogenesis of plaque psoriasis. The proposed dosing schedule is subcutaneous injection once weekly for three weeks followed by every other week injection. To date, brodalumab has not been approved for any indication in the United States. Brodalumab has been recently approved for use in Japan for the treatment of moderate to severe psoriasis. A market authorization application is pending with the European Union.

IV. <u>Clinical Development Plan</u>

The clinical development program for brodalumab for the treatment of moderate to severe psoriasis included the following key phase 2 and phase 3 studies:

- **Study 20090062:** This was a phase 2, multi-center, randomized, double blind, placebocontrolled, multiple dose study in approximately 380 subjects. Subjects were followed for 22 weeks.
- **Study 20120102:** This was a phase 3, multi-center, double-blind, randomized, placebocontrolled with induction, withdrawal, retreatment, rescue, and open-label extension study involving 661 subjects. Subjects were followed for 266 weeks.
- **Study 20120103:** This was a phase 3, multi-center, double-blind, randomized, active comparator (ustekinumab) and placebo-controlled with induction, withdrawal, retreatment, rescue, and open-label extension study involving 2441 subjects. Subjects were followed for 266 weeks.
- **Study 20120104:** This was a phase 3, multi-center, double-blind, randomized, active comparator (ustekinumab) and placebo-controlled with induction, withdrawal, retreatment, rescue, and open-label extension study involving 2509 subjects.

In all, 3207 subjects had greater than 12-months exposure of brodalumab. All phase 3 studies (studies '02, '03 and '04) included a 12 week placebo controlled induction phase, an open-label maintenance phase of 52 weeks, and an open-label long-term extension phase. The phase 2 study (study '62) included a 12-week induction phase, and an open-label extension phase. The study designs allowed for placebo comparison only through the 12-week induction phase. Trial subjects randomized to ustekinumab (study '03 and '04) received it through week 52 of the maintenance phase and then were switched to open-label brodalumab. The sponsor reports that during the 12-week placebo-controlled phase there was no imbalance between brodalumab and
placebo for adverse events, serious adverse events, adverse events leading to discontinuation, and fatal event. There were no completed suicides during the placebo-controlled phases.

In all trials brodalumab was superior to placebo (p<0.001) for the co-primary endpoints (PASI 75 and sPGA of 0 or 1) at week 12. Secondary endpoint analysis also demonstrated superiority. Likewise, brodalumab 210 mg was superior to ustekinumab (p<0.001) for the primary endpoint of PASI 100 at week 12. Overall, the data in support of the efficacy of brodalumab in the treatment of moderate to severe psoriasis is compelling.

Of concern, however, is that during the overall clinical development plan there were an unusually high number of suicides. Cumulatively, there were a total of 39 Suicide Ideation Behavior (SIB) events (SIB includes suicide ideation, suicide behavior, suicide attempt and completed suicide) in 34 subjects, with 12 suicide attempts in 8 subjects, and 6 completed suicides. The following is a summary of the completed suicide cases:

- 58 year old male who participated in a psoriasis study completed suicide by hanging 329 days after beginning treatment with brodalumab, and 58 days after his last dose of brodalumab. The subject had no known psychiatric history; however, on several occasions he stated to the investigator that he was having ongoing financial problems. The subject had a PASI 100 response to treatment.
- 56 year old male who participated in a psoriasis study was found dead in his car soon after completing the trial (14 days after the last dose). The subject was on brodalumab for 97 days. The case was adjudicated to be indeterminate regarding suicidal intent. The medical examiner concluded the event was suicide; however, the investigator concluded that this was an unintentional heroin and alcohol overdose. The subject had a history of depression and anxiety treated with citalopram and alprazolam. Toxicology results identified heroin, alcohol, alprazolam and citalopram. Hospital Anxiety and Depression Scale (HADS) baseline depression and anxiety score decreased from 15 to 2 and 14 to 6, 2 weeks before the event. The subject had a PASI 100 response to treatment.
- 39 year old male who participated in a psoriasis study completed suicide by an unknown method 140 days after the first dose of brodalumab and 27 days after the last dose. He had no known psychiatric history; however, on the last day of the study the subject reported to the investigator that he had some legal problems and would likely be incarcerated soon. The patient had a PASI 75 response to treatment.
- 56 year old male who participated in a psoriasis study completed suicide by jumping from a roof of a building 845 days after his first dose of brodalumab and 19 days after the last dose. The patient had a history of depression and anxiety and was treated with trazodone. During the study the subject reported a brief episode of mild depression. Of note, the subject's Patient Healthcare Questionnaire-8 (PHQ-8) and electronic Columbia Suicide Severity Rating Scale (eC-SSRS) did not identify any suicidal ideation prior to completing suicide. The subject had a PASI 100 response to treatment.
- 57 year old male who participated in an open-label psoriatic arthritis study completed suicide with a gun after 2 years and 7 months of brodalumab treatment. The subject had no known psychiatric history. During the study the subject reported brief episodes of decreased energy. Retrospectively, the investigator learned the subject was having marital difficulties. eC-SSRS and PHQ-8 scores 13 days prior to the event were 0.

• 42 year old female who participated in a rheumatoid arthritis study committed suicide by hanging 118 days after starting treatment with brodalumab. The subject had no known psychiatric history. The subject had reported that she had been experiencing considerable emotional distress related to reproductive and financial issues.

All suicide cases involved subjects treated with brodalumab. Two subjects had a history of a psychiatric disorder to include substance abuse; 4 subjects had no known history of psychiatric disorders. Four subjects completed suicide after stopping brodalumab (14, 19, 27 and 58 days after last dose). In response to the concern about suicide, DDDP obtained the opinion of several groups within CDER.

The Division of Pharmacovigilance (DPV) came to the conclusion that there is "uncertainty about whether the signal for completed suicide is a risk related to brodalumab treatment" and recommended the following options:

- (1) Clear labeling to describe the potential risk of suicide;
- (2) Limiting the product use to second line therapy; and/or
- (3) Implementing risk mitigation strategies.

The Division of Epidemiology I (DEP-I) found that the suicide rate in brodalumab trials was 3 to 4 times higher than in trials for other biological products recently approved for psoriasis. Their recommendations, should brodalumab be approved, included the following:

- (1) Restrict use to patients without a relevant past psychiatric history;
- (2) Clinical monitoring with eC-SSRS and referral when appropriate;
- (3) Consider a Risk Evaluation and Mitigation Strategy (REMS); and
- (4) The Labeling and Medication Guide, as proposed by the sponsor, would help communicate the issue to prescribers and patients; however, post-marketing observational data collection would not be useful given the limitations of such data for suicides.

The Division of Psychiatry Products (DPP) has doubts about the utility of a REMS to prevent suicide and the ability of currently available post-marketing pharmacovigilance methodologies to evaluate this possible signal. DPP recommends the sponsor conduct an active-controlled, parallel group study of at least 52 weeks focusing on frequent monitoring for psychiatric symptoms. DPP believes the proposed trial should be conducted prior to the approval of this BLA.

As described in the Advisory Committee briefing materials, and as discussed at an Advisory Committee, the Division of Risk Management (DRISK) evaluated the sponsor's proposed language for the label and REMS to address the risk of SIB. The proposed labeling includes prescribing information (PI) for healthcare providers (HCP) and a medication guide for patients. Additionally, the proposed Warning and Precaution section of labeling includes statements advising caution when using in patients with a history of SIB and recommends all patients be evaluated for signs of SIB.

In their analysis, DRISK notes that no risk management strategy will completely eliminate the risk of SIB; however, the use of a REMS strategy that includes a medication guide and a communication plan would increase awareness and detection of SIB. Further, DRISK states

that should it be determined that labeling and a communication plan are not sufficient; an "Elements to Assure Safe Use" (ETASU) may be required. ETASUs can include a variety of actions such as (1) requiring prescribers to be trained or specially certified to prescribe the product; (2) requiring special certification for the entity dispensing the drug product; (3) limiting the dispensing to a certain healthcare setting (e.g., in hospital only); (4) limiting drug dispensing to patients with documentation of safe use conditions (e.g., negative pregnancy test); (5) requiring patients be monitored in a particular manner; and (6) enrolling patients in a registry for subsequent assessments. The ETASUs outlined by DRISK for consideration include prescriber certification, pharmacy certification, documentation of safe use, and monitoring requirements.

On July 19, 2016 an Advisory Committee meeting was held to discuss the safety profile of brodalumab and possible approaches to further evaluate safety concerns (i.e., SIB and Major Adverse Cardiovascular Events) identified during the clinical development of brodalumab. During the meeting the sponsor asserted there is no clear association of SIB with brodalumab and proposed the following risk management plan:

- Inclusion of language in the warning and precaution section of labeling reflecting the SIB events and instruction for prescribers to evaluate all patients for signs and symptoms of SIB. Additionally, advice will be included to inform patients and caregiver to seek medical advice if mood changes emerge.
- Enhanced pharmacovigilance to include quarterly safety reviews by an independent safety panel and the use of targeted follow-up questionnaires for SIB cases identified.
- A Medication Guide and Communication Plan to include (1) Dear HCP Letter; (2) Dear Professional Society Letter; (3) HCP Fact Sheet; (4) Patient Wallet Card; (5) HCP Education Brochure; and (6) Website.
- Use of an independent psoriasis registry (i.e., Corrona Psoriasis Registry) to facilitate the conduct of postmarketing comparative safety studies.

Details about the Corrona (Consortium of Rheumatology Researchers of North America) Registry for psoriasis can be found at <u>http://www.corrona.org/registries/psoriasis</u>. The Psoriasis registry was launched in April 2015. It is a joint effort between the National Psoriasis Foundation and Corrona, LLC. Its primary objective is to study comparative safety of psoriasis treatment. Secondary objectives include analyzing the epidemiology and natural history of psoriasis, comorbidities, prescribing practices, and comparative effectiveness. Participation in the Corrona registry is voluntary. Presently, the Corrona registry collects data from 120 dermatologists and 1650 patients. The process includes patients and their providers completing a questionnaire approximately every 6 months. Patients are compensated \$20 for their time. The current Corrona registry captures information on completed suicide and serious suicide attempt, but does not capture data on suicide ideation according to the discussion at the Advisory Committee meeting.

V. Regulatory/Ethical Review

As discussed at the Advisory Committee meeting, there is clear uncertainty as to whether the adverse event SIB is related to the use of brodalumab. Although some of the committee members would not call it a "signal" there was a consensus that more needed to be done to

evaluate the possible connection between brodalumab use and SIB. However, there was concern that a mandatory registry, as part of a REMS, would inappropriately reduce patient access to a potentially useful treatment for moderate to severe psoriasis. We agree the data are incomplete; however, the analysis done by the Division of Epidemiology I showing a 3 to 4 times higher incidence for suicide in brodalumab trials as compared to other biological products recently approved for psoriasis is highly concerning and justifies significant action by the Agency.

As briefly mentioned above, the sponsor has submitted a proposed REMS that will be limited to a medication guide and a communication plan. The proposed REMS does not include any ETASUs or an implementation plan. The sponsor proposes to report REMS Assessments to the FDA 18 months, 3 years, and 7 years from the date of approval of the REMS. The proposed use of the Corrona registry would be outside of the REMS requirement (presumably could be a post marketing requirement if brodalumab is approved). During the Advisory Committee several members suggested the use of a registry should be mandatory. It was clarified during the Advisory Committee that a registry with mandatory participation could only be approved under a REMS.

The Food and Drug Administration Amendments Act (FDAAA), section 505-1 of the Food, Drug, and Cosmetic Act (FDCA) authorizes the FDA to require pharmaceutical sponsors to develop and comply with a REMS for a drug if FDA determines that a REMS is necessary to ensure that the benefits of the drug outweigh the risks. When considering whether a REMS should be required, the FDA is required to consider (1) the size of the population likely to use the drug; (2) the seriousness of the diseases; 3) the expected benefit of the drug; (4) the expected duration of treatment; (5) the seriousness of known or potential adverse events; and (6) whether the drug is a new molecular entity. Given that the size of the population likely to use the drug is potentially large, that moderate to severe psoriasis is a serious condition, the demonstrated benefit of the drug is substantial, the duration of treatment is long (potentially life-long), that SIB is a serious adverse event, and that brodalumab is a new chemical entity, we believe a REMS is appropriate. We agree with the plan to require a medication guide and communication plan as proposed by the sponsor; however, consideration should be given to requiring one or more Elements to Assure Safe Use (ETASUs).

ETASUs may be required as part of a REMS when the FDA determines that a drug is associated with a serious adverse drug experience and can be approved only if, or would be withdrawn unless, such elements are required as part of a strategy to assure safe use. ETASUs can include a variety of actions such as (1) requiring prescribers to be trained or specially certified to prescribe the product; (2) requiring special certification for the entity dispensing the drug product; (3) limiting the dispensing to a certain healthcare setting (e.g., in hospital only); (4) limiting drug dispensing to patients with documentation of safe use conditions (e.g., negative pregnancy test); (5) requiring patients be monitored in a particular manner; and (6) enrolling patients in a registry for subsequent assessments. The purpose of a registry as an ETASU would be to provide information on patients prescribed the drug and allows for follow-up on adverse events and trends. In addition to being a tool to monitor and assess serious adverse events, a registry may be combined with other ETASUs, such as when a registry is used to document that the drug is dispensed to patients with evidence or other documentation of safe-use conditions; or to

document that each patient using the drug is subject to certain monitoring (e.g., eC-SSRS and PHQ-8).

From an ethical perspective, determining whether patient participation in a registry should be voluntary or mandatory will depend upon the relative weight given between two, occasionally competing, ethical principles described in the Belmont Report, namely "respect for persons" and "beneficence." The Belmont Report describes "respect for persons" as incorporating the ethical principle that "individuals should be treated as autonomous agents." Autonomy can be considered as an inherent right to self-determination that is free from controlling influences by others and personal limitations preventing meaningful choice. The Belmont Report describes "beneficence" as an obligation to (1) "do no harm" and (2) "maximize possible benefits and minimize possible harms." Although both a voluntary registry and a mandatory registry could be designed to require informed consent (a common way in which respect for persons is demonstrated), the use of a registry that requires mandatory participation in order to obtain access to the drug product could be considered an inappropriate controlling influence that prevents meaningful choice and self-determination absent sufficient justification supporting mandatory participation. In the situation at hand, the decision between whether there should be a ^{(b)(4)} or a registry in which participation is mandatory voluntary registry in order to obtain access to brodalumab depends on how necessary a registry is to ensure the benefits of the drug outweigh the risks of the drug, and which type of registry offers the best possibility in mitigating the risk of SIB.

In our opinion, the utility of the voluntary Corrona registry in mitigating risk of SIB is severely limited by its design and scope of coverage. As presently designed and functioning, the Corrona Psoriasis Registry is limited to dermatologists and patients willing to participate, and assesses adverse events only twice yearly with a questionnaire that does not capture information on all elements of SIB (i.e., suicidal ideation not captured according to statements made at the Advisory Committee). As stated at the Advisory Committee meeting, only 120 dermatologists are presently engaged in the Corrona registry. This represents only a small fraction of the 9,600 dermatologists believed to be practicing in the United States and fails to consider other medical specialties that might prescribe brodalumab should it be approved¹. Similarly, the Corrona Psoriasis Registry presently has only 1650 psoriatic patients enrolled; which likewise represents only a small fraction of patients with moderate to severe psoriasis. Given these limitations, a mandatory registry under a REMS would permit a better opportunity to identify cases of SIB in patients using brodalumab and could allow for improved monitoring.

In summary, we believe a registry in which mandatory participation is required in order to obtain access to brodalumab is ethically justifiable under a REMS, if such a registry were designed appropriately to assure the safe use of brodalumab. The concern about how a restrictive REMS program would impact access to the biologic drug product is a reasonable concern; however, we note there are several highly effective treatments already available on the U.S. market and believe the choice in prescribing brodalumab should be made cautiously given the possibility its use might increase the risk of SIB. The REMS could be removed at some point in the future if the risk of SIB is found to be less of a concern.

¹ Source: "Harris William & Co. Dermatology Overview available at <u>http://www.harriswilliams.com/system/files/industry_update/dermatology_market_overview.pdf</u>

On August 8, 2016 a meeting was held of the REM Oversight Committee (ROC) to discuss the following two questions:

- 1. Given the potential signal for SIB observed with brodalumab, is risk mitigation beyond optimized labeling necessary for approval?
- 2. Assuming that labeling will include a Boxed Warning, which of the following risk management options do you recommend for brodalumab?
 - a. REMS with communication plan (CP), with option to modify to increase ETASU based on results of 18-month assessment
 - b. REMS with ETASU.

The committee was presented the opinions of the various groups involved with the review of this application and the pros and cons of various options were discussed. The group agreed that moderate to severe psoriasis a serious condition and that alternative treatment options are needed. However given the uncertainty associated with the 6 completed suicides, most members of the ROC agreed there was adequate justification for a REMS with an ETASU. We agree with this position. The issue of a voluntary versus a mandatory registry was not addressed during the meeting.

Thank you for the consult.

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

/s/

KEVIN A PROHASKA 08/10/2016

ROBERT M NELSON 08/10/2016



DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration 10903 New Hampshire Avenue Silver Spring, MD 20993-0002

Date: From:	June 23, 2016 Janice Ferguson, RN, BSN CDRH/ODE/GHDB
То:	Strother Dixon Regulatory Health Project Manager OMPT/CDER/OND/ODEII/DDDP
CC:	Gary Chiang Medical Officer OMPT/CDER/OND/ODEIII/DDDP
Subject:	BLA761032 Brodalumab (SILIQ™) 210mg in 1.5mL solution (140mg/mL) in one Single-use PFS Valeant Pharmaceuticals

Recommendation: CDRH recommends BLA approval of the device constituent part of the brodalumab pre-filled syringe.

1. Purpose of Memo and Review Summary:

CDER has requested that CDRH provide a device review and written comments on the delivery system for BLA761032 Brodalumab and attend any meetings (internal and sponsor meetings).

It is unclear if CDRH if provided comments for any IND for combination product.

The device constituent part of this combination product is a 2.25 mL pre-filled syringe (PFS) with a deliverable volume of 1.5mL.

Brodalumab is a monoclonal antibody antagonist to human IL-17 receptor A (IL-17RA). The proposed dosing regime is 210 mg subcutaneously at weeks 0, 1, and 2, followed by 210 mg every 2 weeks (Q2W).

Brodalumab is indicated as a single agent prescription drug product for the treatment of adult patients with moderate to severe plaque psoriasis who are candidates for systemic therapy or phototherapy. Psoriasis is a chronic, common immune-mediated inflammatory skin disease associated with substantial impairment of physical and psychological quality of life.

The CDRH reviewer performed an evaluation of the device constituent part of the brodalumab Pre-filled Syringe (PFS). The device is a 2.25 mL $^{(b)(4)}$ syringe with a 27G x ½ inch staked needle. The syringe will be filled with 1.5 mL of the drug product at a concentration of 140 mg/mL for a total dose of 210mg.

The applicant provided performance testing for the PFS needle and needle and syringe combination. Needle shield removal force, needle pull out force and needle injection depth data was provided and met the acceptance criteria. The needle and syringe combination functional testing was provided. Deliverable volume, Breakloose and extrusion force all met the acceptance criteria.

The quality attributes of the device constituent part of the combination product are deliverable volume,

Breakloose and extrusion force and lot release testing was provided with test methods and acceptance criterial to assure the quality of the drug product.

The deliverable volume is monitored through real-time testing through evaluation of the in-process fill weigh checks of individual syringes. The acceptance criterion is between ^(b)₍₄₎ mL and ^{(b) (4)}mL for the 1.5 mL PFS. This ensures that sufficient volume is dispensed to meet the label claim and minimize excess volume.

The Breakloose and extrusion ensure that the physical forces required to expel the contents of the prefilled syringe are within acceptable limits. The acceptance limit of $^{(b)}$ N for lot release is aligned with the device verification criteria. Drug product lot release results for Breakloose and extrusion are 3 to 6 N and 5 to 13 N, respectively. This is well below the acceptance criteria of $^{(b)}$ N.

It was observed that there were no significant trends observed in the Breakloose and extrusion during stability when the drug product is stored at the recommended conditions, therefore breakloose and extrusion will not be included in the stability program.

Review outcomes/Recommendations

There are no outstanding device issues. CDRH recommends BLA approval of the device constituent part of the brodalumab pre-filled syringe.

Consultants for this file

Kiros Hailemarian, PhD-biocompatibility reviewer

The review covered the following review content

Functionality of Pre-filled syringe Biocompatibility of the syringe barrel, needle, needle shield and plunger rod Device constituent part usability or human factors validation information

The review did not cover the following items

Review of drug product Manufacturing of the drug product Review of the primary container closure-drug product interaction toxicology including plunger stopper Review of the safety and efficacy of drug product after contacting the device constituent parts or while stored in the device constituent parts, including extractable analysis Manufacturing of the device constituent part of the combination product Review of the final drug kit packaging Manufacturing of the device constituent part of the combination product Shipping of the final kit package Mechanical loss testing for the drug product Stability of the drug product after aging Sterility of the container closure system

2. Documents Reviewed and References

CDRH/ODE reviews content related to the design of device constituent parts for combination product submissions. This review is limited to design requirements and verification validation information to support the device constituent part, including essential performance of the device constituent part and reliability of the device constituent part over time and after expected environmental exposure. This review does not cover review of the primary "container closure" (I.e. cartridge), manufacturing or process validation of the device, nor usability.

BLA761032 Information request from BD dated 3/11/2016

3. Background

AstraZeneca submitted a BLA for brodalumab injection, for subcutaneous use. Brodalumab is a monoclonal antibody antagonist to human IL-17 receptor A (IL-17RA). The efficacy and safety of brodalumab was supported by clinical trials. Pre-BLA meetings were held March 25, 2015, May 13, 2015 and October 2015. It is not known if CDRH was consulted and gave advice for any of those meetings. Amgen was the sponsor of the covered clinical studies at the time they were carried out with transfer of sponsorship to AstraZeneca for the psoriasis IND104671 on September 1, 2015. On April 1, 2016 AstraZeneca transferred all rights and ownership to Valeant Pharmaceuticals Luxembourg S.a.r.I.

4. Review

Product description

Brodalumab is a human monoclonal IgG2 antibody antagonist to human IL-17 receptor A (IL-1RA). The proposed dosing regime is 210 mg subcutaneously at weeks 0, 1, and 2, followed by 210 mg every 2 weeks (Q2W).

The drug product is supplied as a sterile, single-use, preservative-free solution for subcutaneous injection in a PFS. It contains 140 mg/mL in a 2.25 mL syringe filled to deliver a volume of 1.5 mL to provide the dose of 210mg of brodalumab.

Indications for Use

Brodalumab is indicated as a single agent prescription drug product for the treatment of adult patients (18 years or older) with moderate to severe plaque psoriasis who are candidates for systemic therapy or phototherapy.

It may be self-administered or administered by a care giver or healthcare provider in a clinical or non-healthcare environment. The subcutaneous sites of administration are the arm, abdomen, or thigh.

Device Description

The primary container closure cor	sists of a 2.25 mL glass (Ty	pe 1) syringe with	a staked in place stainless	s
steel needle covered with	^{(b) (4)} needle shield and a		^{(b) (4)} plunger-stopper	
laminated with a fluoropolymer filr	n on the product contact sur	face. The	(b) (4) needle shield protects	6
the needle cannula and may be su	upplemented with an	^{(b) (4)} rigid needle	shield cover. (b) (4)	
			(b) (4)	
		^{(b) (4)} . A plas	tic plunger rod is threaded	
into the plunger-stopper. The syrir	nge flange is supplied with a	plastic flange ext	ender.	

The 2.25 mL syringes are supplied		^{(b) (4)} . The plunger-
stoppers are supplied	(b) (4)	

No graduation marks are needed on the PFS because the filled volume has been verified and the labeled deliverable volume is intended to be delivered with one injection, i.e., the PFS is single use for a fixed dose.

The ^{(b) (4)} PFS allows the user to inspect the drug appearance prior to injection and also to confirm that the injection has been completed.

The PFS includes a needle shield to help protect the patient from injury and the system from damage. The needle shield protects and maintains the container closure and sterility of the needle before use and protects the needle from damage. The needle shield also provides some protection to the user from needle stick injury prior to injection. *Of note: other than the needle shield this PSF does not contain a passive or active sharps injury prevention feature.*

All components, except the plunger rod, flange extender and the needle shield outer plastic cover, have surfaces that come into contact with the drug product. These components constitute the fluid path.



Components and Composition of the Primary Container Closure System (1 mL Long and 2.25 mL Syringes)



		Specifi	cation	
Component	Parameter	1.0 mL Long Syringe System	2.25 mL Syringe System	Test Method
Syringe barrel with	Material requirements	Type I glass PhEur 3.2.1	USP<660> / I / JP 7.01	Manufacturer's certificate
staked needle. (b) (4)	Barrel inner diameter (I.D)		(6) (4)	Measurement
	(b) (4))		Measurement
				Measurement
				Manufacturer's certificate
				Manufacturer's certificate
				Manufacturer's certificate
Plunger- stopper	Material requirements	Conformance t PhEur	o USP<381>/ 3.2.9	Manufacturer's certificate
			(b) (4)	Manufacturer's certificate
	Outer diameter (b) (4)			Measurement
'	Trim outer diameter			Measurement
	Overall length			Measurement
Needle shield	Material requirement	Conformance t PhEur 3.2.9	o USP <381>/ / USP<87>	Manufacturer's certificate

Syringe Barrel, Plunger-stopper, and Needle Shield Primary Container Closure Component Specifications

Conditions of Use/Mechanism of Action

PFS Conditions of Use

Biologic product for injection	brodalumab only, for subcutaneous injection
Dosage capability	Single dose: 1.5 mL
Method of injection	Manual delivery
Environment of use conditions	Non-Healthcare or Clinical Environments
Recommended Storage	Store refrigerated at 2°C to 8°C (36°F to 46°F) in the original carton. Do not freeze.
Handling	Acclimate to room temperature by setting out at room temperature for at least 30 minutes. Protect from direct sunlight.

The Pre-filled syringe is a manual system. Needle insertion and drug delivery are both achieved by userapplied force.

Reviewer Comment:

No graduation markings are needed on the PFS as the filled volume is verified and the labeled volume is intended to be delivered in one injection. The PFS is a single used for a fixed dose. The design of the PFS (clear glass) allows the user to inspect the drug appearance prior to injection and to confirm that the injection is complete. The PFS includes a needle shield to help protect the patient from injury and the system from damage. The needle shield protects and maintains the container closure and sterility of the needle before use and protects the needle from damage. The needle shield also provides some protection to the user from needle stick injury prior to injection. *Of note: there is not a passive or active sharps injury prevention feature on this pre-filled syringe.*

Standards Utilized

Document Number	Year Published	Document Title
ISO 10993-1	2009	Biological Evaluation of Medical Devices – Part-1Evaluation and Testing Within a Risk Management Process
ISO 10993-5	2009	Biological Evaluation of Medical Devices – Part 5: Tests for in vitro cytotoxicity
(b) (4)	2008	Biological evaluation of medical devices – (b) (4)
ISO 10993-10	2011	Biological Evaluation of Medical Devices – Part 10: Tests for irritation and skin sensitization
ISO 15223-1	2012	Medical Devices-Symbols to Be Used With Medical Device Labels, Labeling and Information to Be Supplied-Part 1: General Requirements
EN 1041	2008	Information supplied by the manufacturer of medical devices
IEC 62366	2007	Medical Devices – Application of Usability Engineering to Medical Devices
ISO 11040-4	2007	Prefilled Syringes – Part 4: Glass Barrels for injectables
ASTM D4169	2009	Standard Practice for Performance Testing of Shipping Containers and Systems.
ISO 14971	2009	Medical devices – Application of Risk Management to Medical Devices.
EN 556-1	2007	Sterilization of Medical Devices – Requirements for Medical Devices to be Designated "Sterile" – Part 1. Requirements for Terminally Sterilized Medical Devices.
ASTM F1980	2007	Standard Guide for Accelerated Aging of Sterile Barrier Systems for Medical Devices
(b) (4)	2009	Microbiological Aspects (b) (4).
(b) (4)	2007	Sterilization of Health Care Products – (b) (4) (b) (4)
ISO 11137-1	2006	Sterilization of health care products – Radiation – Part 1: Requirements for development , validation, and routine control of sterilization process for medical devices.
ISO 11137-2	2012	Sterilization of health care products – Radiation – Part 2: Establishing the sterilization dose (2012).
ISO 11137-3	2006	Sterilization of health care products – Radiation – Part 3: Guidance on dosimetric aspects
(b) (4)	2006	Sterilization of health Care products – Biological indicators –

Standards Applicable to PFS

ASTM F1929:	2012	Standard Test Method for Detecting Seal Leaks in Porous Medical Packaging by Dye Penetration.
ASTM F2096	2011	Standard Test Method for Detecting Gross Leaks in Medical Packaging by Internal Pressurization (Bubble Test).
ASTM F88/F88M	2009	Standard Test Method for Seal Strength of Flexible Barrier Materials
ASTM F1886-M	2009	Standard Test Method for Determining Integrity of Seals for Flexible Packaging by Visual Inspection
FDA Guidance	2013	Use of International Standard ISO-10993, "Biological Evaluation of Medical Devices Part 1: Evaluation and Testing" Draft Guidance for Industry and FDA Staff
FDA Guidance	2013	Draft Guidance - Glass Syringes for Delivering Drug product and Biological Products: Technical Information to Supplement International Organization for Standardization (ISO) Standard 11040-4
FDA Guidance	2013	Guidance - Technical Considerations for Pen, Jet, and Related Injectors Intended for Use with Drugs and Biological Products

Sterility

The sterility of the needle and microbial aspect overall container closure integrity (^{b) (4)}) is being reviewed by CDER. (Per email of Mathew White 2/22/2016).

(b) (4)

Biocompatibility

Component	Material	Drug Product Contacting (Fluid Path)	User Contacting
Barrel (with integral shoulder, flange)	Type 1 Glass (per USP<660>/PhEur 3.2.1/JP 7.01); (b) (4)	Yes	Yes
Needle	(b) (4) _{Stainless Steel;} (b) (4)	Yes	Yes
Plunger-stopper	(b) (4	Yes	No
Non-rigid needle shield	(b) (4)	Yes	Yes
Needle shield outer plastic cover	(b) (4)	No	Yes
Flange extender	(б) (4)	No	Yes
Plunger rod	(b) (4)	No	Yes

PFS Description of Components and Materials of Construction

Externally Communication Device, blood path-indirect limited < 24 hour contact
(b) (4) 2.25 mL Syringe Barrel w/ 27 G 1/2 inch needle & Rigid Needle
shield
Cytotoxicity
Sensitization
Intracutaneous Reactivity
Acute Systemic Toxicity
Hemocompatibility
Rabbit Material-mediated pyrogenicity tests

Surface (skin) contacting limited < 24 hours contacting limited >	ct
Plunger rod & flange extender	
Cytotoxicity	
Sensitization	
Intracutaneous Reactivity	

Reviewer Comment:

This glass syringe/needle and shield are externally communicating devices, blood path-indirect with a limited exposure of less than 24 hours. An information request was sent to $^{(b)(4)}$ to obtain the information as only a certificate of compliance was submitted. An information request was sent t for this information on March 9, 2016.

The plunger rod and flange extender is skin contacting with limited exposure of less than 24 hours.

On March 11, 2016 ^{(b) (4)} provided a biocompatibility testing for the ^{(b) (4)}2.25 mL with 27g ¹/₂ inch needle for cytotoxicity, sensitization, intracutaneous Reactivity, Acute Systemic Toxicity and Hemocompatibility.

The CDRH biocompatibility consultant reviewed the data provided in the information request and the information in the submission for the combination product and determined that there are no outstanding issues. The sponsor performed the following tests: cytotoxicity, irritation, sensitization, acute systemic toxicity, hemocompatibility, rabbit material-mediate pyrogenicity tests and the results of these tests are acceptable. In addition, the sponsor performed chemical analysis (leachables/extractables), and the results are acceptable. The Limulus Amebocyte Lysate (LAL) test is being reviewed by CDER per the communication from CDER 2/22/2016.

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Reviewer Comment:

All functional/performance verification test units were exposed to simulated transportation, per ASTM D4169 transportation conditions.

The functional testing results included: Breakloose and Extrusion forces, deliverable volume and the addition of needle insertion depth.

The Breakloose and Extrusion forces (BLE) of the 1.5 mL fill brodalumab PFS presentation were Newton's under anticipated conditions of use. Test articles were production equivalent Sixty (60) 1.5 mL fill PFS with rigid needle shield were tested.

The sponsor stated in their application that they did additional testing regarding needle depth $^{(b)}(4)$ mm. An information request was sent to the applicant on April 7, 2016, on April 14, 2016 the sponsor provided a response. A "Tolerance Analysis Report" was provided. The data provided by the sponsor for the PFS with a 27g ½ inch needle is capable of delivering a subcutaneous injection at a depth of $^{(b)}(4)$ mm at a 45 ° angle as well as a 90° angle. (a more thorough sponsor response was provided at the end of this memo.

IR to applicant on 6/14/2016 regarding needle performance:

The syringe supplier has provided batch record summary data from recent production of the supplier's syringe barrel batch 6120737. These data are representative of typical production results from the validated processes for the 2.25mL (b) (4) barrel with rigid needle shield

^{(b) (4)} The complete sponsor response is located in Section 6 Interactive Review. The applicant has provided summary results

A certificate of conformance was provided by ^{(b) (4)} in the application for the ^{(b) (4)} 2.25 ml x 27G ¹/₂ inch staked needle. The needle conforms to the AISI 304 standard. In addition, the syringe barrel undergoes various in process and final inspections to include: ^{(b) (4)}

The applicant provided functional testing for the syringe, Breakloose and extrusion force, deliverable volume and needle insertion depth validation. Additional information was obtained regarding the rigid needle shield (b) (4)

^{(b) (4)}. All of these test results are reported as passed and are within the device specifications.

The functional/performance testing provided by the applicant demonstrates that the PFS will function for its intended use as the device constituent part of this combination product.

Device Design Validation

Design validation for human interface and labeling was conducted through formative and summative testing. Design validation has established, by objective evidence, that the 2.25 mL syringe with a volume of 1.5mL, meets all the documented user needs, and is safe and effective for use by the intended user population. The design validation protocol was developed based on design inputs, including user needs and the Design Validation Plan.

See Risk Management

(b) (4)

Lot Release

Deliverable Volume

The prefilled syringe (PFS) drug product lot release specification limits for deliverable volume ensure sufficient volume is dispensed to meet label claim via a lower specification limit and minimize excess volume according to USP <1151> guidance by incorporating an upper specification limit . Results that meet the specification acceptance criteria are reported as "pass".

Volume Lot Release Specification Acceptance Criteria

Presentation	Specification	Lower Acceptance Criteria	Upper Acceptance Criteria
1.5 mL	Pass	^{(Ե) (4)} mL	^{(b) (4)} mL

Lot Number	Label Claim (mL)	Number of Syringes (fill weight)	Mean Fill Weight (g) ° (Min – Max)	Mean Deliverable Volume by Fill Weight (mL) ^b (Min-Max)	Mean Deliverable Volume by Compendial Method (mL) ^c (Min-Max)
0010225385		*			(b) (4
0010225386					
0010225387					
0010225378					
0010225379					
0010225380					
0010225382					
0010225389					
0010225383					
					(b) (

(b) (4)

Breakloose and Extrusion

Breakloose and extrusion are included in the specification to ensure that the forces required to deliver brodalumab are within acceptable limits. Breakloose and extrusion are the physical forces required to expel the contents of a prefilled syringe. The breakloose force is the force required to overcome the static coefficient of friction and start the syringe plunger moving inside of the barrel. The extrusion force is the maximum force required to move the plunger sufficiently down the syringe barrel to expel the entire contents through the needle.

	Extrusion												
Functionality	Product- Related Impurities Detected	Historical Lot Range	Stability Trend (Y/N)	Statistically Derived Limit	Release Specification	Stability Specification							
Breakloose (N)	None (Functionality)				(b) (4	No							
Extrusion (N)	None (Functionality)					No							

Drug Product Lot Release Results Summary for Breakloose and

The acceptance limit of ^{(b) (4)} N for lot release and stability align with the device design verification criteria, and is based on the maximum acceptable expression force preferred by healthcare workers in a prefilled syringe expression force comparative usability study.

Breakloose and extrusion forces together determine the force needed to extrude the contents of the syringe; therefore a single specification limit applies to both. This specification is appropriate to ensure the forces required to deliver brodalumab are within acceptable limits.

Lot Number	Breakloose (N)	Extrusion (N)
0010090623		(b) (4)
0010110558		
0010111478		
0010111891		
0010122996		
0010126956		
0010128195		
0010128232		
0010129878		
0010129939		
0010130271		
0010132980		
0010132985		
0010132994		
0010132995		
0010137090		
0010140165		
0010140336		
0010149109		

Lot History Breakloose and Maximum Extrusion Force

Lot History E	Breakloose and Maximum	Extrusion Force
Lot Number	Breakloose (N)	Extrusion (N)
0010149112		(b) (4)
0010149140		
0010149153		
0010149625		
0010156192		
0010157233		
0010158066		
0010158967		
0010158969		
0010158972		
0010159531		
0010168783		
0010168801		
0010168809		
0010168833		
0010168835		
0010173712		
0010174703		
0010174716		
0010177700		
0010177705		
0010180705		
0010180709		
0010180836		
0010183900		
0010189194		

Historical lot release and stability data from the clinical and commercial scale batches were evaluated to estimate ranges that will contain approximately 99% of the population with 95% confidence. The historical data used is in the tables below. This data is used to predict the long-term expected behavior of the device functionality. To access changes during stability, the stability data from long term storage at the recommended storage temperature was combined with the lot release data. There were no practically significant trends observed in either breakloose or extrusion during stability monitoring for the prefilled syringe drug product when stored at the recommended condition.

The applicant states that the breakloose and extrusion will not be included in the stability program, since no statistically significant trends were observed

Reviewer Comment:

The quality attributes of the device constituent part of the combination product are deliverable volume, Breakloose and extrusion force and lot release testing was provided with test methods and acceptance criterion to assure the quality of the drug product.

The deliverable volume is monitored

The acceptance criterion is between ^{(b) (4)}mL and ^{(b) (4)}mL for the 1.5 mL PFS.

This ensures that sufficient volume is dispensed to meet the label claim and minimize excess volume.

The Breakloose and extrusion ensure that the physical forces required to expel the contents of the prefilled syringe are within acceptable limits. The acceptance limit of ^{(b) (4)} N for lot release is aligned with the device verification criteria. Drug product lot release results for Breakloose and extrusion are ^{(b) (4)} R. It was observed that there were no significant trends observed in the Breakloose and extrusion during stability when the drug product is stored at the recommended conditions, therefore breakloose and extrusion will not be included in the stability program.

(b) (4)

Packaging

Labeled single-use syringes are placed into plastic trays. Each tray is placed into a paperboard carton with its corresponding leaflets and container closure label. Each carton is constructed of solid paperboard that shields the product from light.

Shipping studies

Output Tested	Design Input Trace	Post Inspection Pass	Post Inspection Fail
Carton remains intact	PS-003166	60/60	0/60
Tray remains intact	4.11, 4.3.1,	60/60	0/60
No external damage to the carton that potentially affects functionality of the syringe/device. No visible damage to the PFS	4.3.2,4,5.1 RS-002989 827 PES3 6	60/60	0/60
No syringe breakage/cracks. No visible damage to the PFS		60/60	0/60
Carton closure label adhered to carton and clear visual evidence of carton closure label removal (e.g. integrated tamper evident fibers of the carton closure label broken or missing, changing appearance of the carton closure label	RS-003166 4.10.1	60/60	0/60
Plunger stopper and Plunger rod remain assembled		60/60	0/60
Flange extender remains assembled to formed flange of PFS-SA	RS-002909	60/60	0/60
Needle shield remains assembled to needle hub of syringe barrel of the PFS-SA	827PFS3.4	60/60	0/60
Primary label remains on the syringe barrel of the PFS-SA		60/60	0/60
Primary label allows the user to view the drug product along the axial length of the PFS syringe barrel	RS-002909 827PFS6.8	60/60	0/60
Label text and artwork are legible after distribution testing	RS-002909 827PFS6.10	60/60	0/60

Shelf life/Stability

Stability Storage Conditions for the Prefilled Syringe

Temperature	Range	Condition
5°C	2°C to 8°C	Recommended
25°C	23°C to 27°C	Accelerated
30°C	28°C to 32°C	Accelerated
40°C	38°C to 42°C	Stressed

Storage Condition and Testing Time Points for Brodalumab Primary and Supporting Lot Stability Program

									Time	Points							
Temperature	0 ³	1 DAY	3 DAY	1 WK	2 WK	з wк	1 MO	6 WK	2 MO	3 MO	6 MO	9 MO	12 MO	18 MO	24 MO	36 MO ^b	48 MO ^b
2°C to 8°C	x									х	х	х	x	x	x	x	×
25°C	x			Xq	x		×	Xh	Xª	x	×						
30°C/65% RH*	х			х	х		x	x	x	х							
40°C	х	Xe	Xc	х	х	X ^h	X			X							

 WK = Week, MO = Month, RH = Relative Humidity
 Release results may be used for stability T=0 time point for all storage conditions.
 To support storage of brodalumab drug product at room temperature, 34 and 46 month points were added to lots 0010069787, 0010069783 and 0010069779. Lot 0010054225 and 0010054227 has an additional 42 month time point.
 A strained to be the point for all storage on point for all storage conditions. 0010054225 and 0010054227 has an additional 42 month time point. ⁶ Applicable to lots 0010054225, 0010054227, 0010069780, 0010069780, 0010069782, 0010159531 and 0010193493 only. Lot 0010187933 and 0010201816 were tested at T=3 DAY only. ^d Applicable to lots 0010059781, 0010069780, 0010059531 and 0010069782 only. ^e Applicable to lots 0010159531, 0010193493 and 0010187933 only. Storage temperature for lot 0010201816 was 30°C [†] 1 MO not applicable to lots 0010159531, 0010193493 and 0010187933. ⁹ Applicable to lots 0010159531, 0010193493 and 0010187933. ^h Applicable to lot 0010059531 only.

Stability	Test	Schedule	for the	Brodalumab	PFS	Primary	and	Productio	on
			Lots	at 5°C					

Time Point (Months)										
Test Method	0 ^a	1°	3	6	9	12	18	24	36	48
Appearance	Х	Х	Х	Х	х	Х	X	Х	Х	х
Color	Х	х	X	X	Х	Х	x	х	Х	Х
Clarity	Х	X	X	х	х	X	X	х	X	х
cIEF	Х	x	х	х	X	х	X	х	х	х
SE-HPLC	Х	x	x	x	x	X	x	x	х	х
rCE-SDS	Х	х	X	X	х	х	х	X	Х	х
nrCE-SDS	Xd	Xd	Xd	Xd	X	Х	х	Х	X	х
Sterility	Xb	x	_	—	_	х	_	х	х	х
CCI	X°		-	-	-	х		х	х	X
Potency	Х	х	Х	Х	Х	Х	х	Х	Х	Х
pН	Х	x	х	х	X	х	X	х	х	х
Subvisible particles	X	x	x	x	x	x	x	x	x	х
Breakloose and extrusion	X°	Xc	Xc	Х	—	Х		Х	Х	Х

^a Release results used for stability T=0 time points. For product lots first timepoint is at 1 month.
 ^b Sterility tested at lot release only for the production lots.

° Tested for the production lots only.

^d nrCE-SDS was added to the stability program starting at 9 months for the primary lots.

Summary of Lots in the Stability Program

Drug Product Lot Number	Drug Product Strength (mg/mL)	Drug Product Manufacturing Site	Drug Product Date of Manufacture	Fill Volume	Primary container (PFS) size	Drug Substance Lot Number	Drug Substance Manufacturing Site	Stability Program	Latest Stability Time Point (Months)
0010054225	140	(b) (4)	30 Jun 2010	1.0 mL	1 mL	30051710	(b) (4)	Supporting	48
0010054227	140		30 Jun 2010	0.5 mL	1 mL	30051710		Supporting	48
0010069781	140		03 Dec 2010	0.5 mL	1 mL	0010064015		Primary	48
0010069784	140		09 Dec 2010	0.5 mL	1 mL	0010066965		Primary	48
0010069787	140		20 Dec 2010	0.5 mL	1 mL	0010066968		Primary	48
0010069780	140		02 Dec 2010	0.75 mL	1 mL	0010064015		Primary	48
0010069783	140		08 Dec 2010	0.75 mL	1 mL	0010066965		Primary	48
0010069786	140		17 Dec 2010	0.75 mL	1 mL	0010066968		Primary	48
0010069779	140		01 Dec 2010	1.0 mL	1 mL	0010064015		Primary	48
0010069782	140		07 Dec 2010	1.0 mL	1 mL	0010066965		Primary	48
0010069785	140		17 Dec 2010	1.0 mL	1 mL	0010066968		Primary	48
0010159531	140		27 Jun 2013	1.0 mL	1 mL	0010164743		Supporting	18
0010193493	140		29 Jan 2014	1.5 mL	2.25 mL	0010193170		Primary	12
0010187933	140		28 Jan 2014	1.5 mL	2.25 mL	0010193080		Primary	12
0010201816	140		17 Jun 2014	1.5 mL	2.25 mL	0010187787		Primary	6
								(b) (4)	Page 1 of 2

Summary of Lots in the Stability Program

Drug Product Lot Number	Drug Product Strength (mg/mL)	Drug Product Manufacturing Site	Drug Product Date of Manufacture	Fill Volume	Primary container (PFS) size	Drug Substance Lot Number	Drug Substance Manufacturing Site	Use	Latest Stability Time Point (Months)
0010225385	140	(b) (4)	29 Oct 2014	0.75 mL	1 mL	0010164743 0010177627	(b) (4)	Production*	3
0010225386	140		03 Nov 2014	0.75 mL	1 mL	0010164743 0010177627 0010177628		Production*	3
0010225387	140		05 Nov 2014	0.75 mL	1 mL	0010164743		Production*	3
0010225380	140		21 Oct 2014	1.0 mL	1 mL	0010177627		Production*	3
0010225378	140		23 Oct 2014	1.0 mL	1 mL	0010164743		Production ^a	3
0010225379	140		27 Oct 2014	1.0 mL	1 mL	0010164743 0010177627 0010177628		Production ^a	3
0010225382	140		11 Nov 2014	1.5 mL	2.25 mL	0010164743		Production ^a	3
0010225389	140		13 Nov 2014	1.5 mL	2.25 mL	0010177628		Production*	3
0010225383	140		17 Nov 2014	1.5 mL	2.25 mL	0010164743 0010177627 0010177628		Production*	3
								(b) (4)	Page 2 of 2

	Stability						
Test Method	Acceptance Criteria	0	3 MO	6 MO	9 MO	12 MO	18 MO
Breakloose Force (N)	_						(b) (4)
			·			5 5 555	

Stability Data for 1.5 mL Fill PFS Brodalumab Drug Product Primary Lot 0010193493 (5°C Horizontal)

Stability Data for 1.5 mL Fill PFS Brodalumab Drug Product Primary Lot 0010193493 (5°C Horizontal)

	Stability	Time							
Test Method	Acceptance Criteria	0	3 MO	6 MO	9 MO	12 MO	18 MO		
Extrusion Force (N)	_						(4)		

Stability Data for 1.5 mL Fill PFS Brodalumab Drug Product Primary Lot 0010187933 (5°C Horizontal)

	Stability	Time					
Test Method	Acceptance Criteria	0	3 MO	6 MO	9 MO	12 MO	18 MO
Breakloose Force (N)	-						(b) (4)

Stability Data for 1.5 mL Fill PFS Brodalumab Drug Product Primary Lot 0010187933 (5°C Horizontal)

	Stability	Time					
Test Method	Acceptance Criteria	0	3 MO	6 MO	9 MO	12 MO	18 MO
Extrusion Force (N)	_						(b) (4)

.

Test Method	Stability	Time					
	Acceptance Criteria	0	3 MO	6 MO	9 MO	12 MO	
Breakloose Force (N)	-			1		(b) (4	

Stability Data for 1.5 mL Fill PFS Brodalumab Drug Product Primary Lot 0010201816 (5°C Horizontal)

Stability Data for 1.5 mL Fill PFS Brodalumab Drug Product Primary Lot 0010201816 (5°C Horizontal)

Test Mathed	Stability	Time					
Lest Method	Acceptance Criteria	0	3 MO	6 MO	9 MO	12 MO	
Extrusion Force (N)	-					(b) (4)	

Stability Data for 1.0 mL Fill PFS Brodalumab Drug Product Primary Lot 0010069779 (5°C Horizontal)

	Stability		Tin	ne	
Test Method	Acceptance Criteria	0	3 MO	6 MO	9 MO
Breakloose Force (N)	_				(b) (4)

Stability Data for 1.0 mL Fill PFS Brodalumab Drug Product Primary Lot 0010069779 (5°C Horizontal)

	Stability			Time		
Test Method	Acceptance Criteria	12 MO	18 MO	24 MO	36 MO	48 MO
Breakloose Force (N)						(b) (4)

	Stability				
Test Method	Acceptance Criteria	0	3 MO	6 MO	9 MO
Extrusion Force (N)	-				(0) (4)

. Stability Data for 1.0 mL Fill PFS Brodalumab Drug Product Primary Lot 0010069779 (5°C Horizontal)

Stability Data for 1.0 mL Fill PFS Brodalumab Drug Product Primary Lot 0010069779 (5°C Horizontal)

	Stability					
Test Method	Acceptance Criteria	12 MO	18 MO	24 MO	36 MO	48 MO
Extrusion Force (N)	_					(6) (4

Reviewer Comment:

The performance of the PFS after aging was evaluated. The tables above represent the 3 lots of drug product/PFS in the 1.5 mL fill (2.25 mL syringe presentation) through 12 months and one lot of the 1.0 fill (1.0 mL syringe presentation though 48 months.

The 1.5 mL drug product presentation filled in the 2.25 mL glass syringe was developed after the 0.5 mL, 0.75 mL and 1.0 mL PFS. Analytical comparability was demonstrated that shows similar product quality attributes and degradation rates to the drug product filled in the 1 mL Long syringe (0.75 mL and 1.0 mL). Therefore, the proposed expiry of ${}^{(b)}_{(4)}$ months is applied to the 1.5 mL prefilled syringe drug product presentation stored at the recommended storage condition of 5°C.

Breakloose and extrusion Force for all time points was well below the acceptance criteria of ^{(b) (4)}N.

An information request was sent to the sponsor on April 7, 2016 regarding data for deliverable volume at the end of shelf life. A response from the sponsor was received on April 14, 2016 and can be found in its entirety at the end of this memo.

The deliverable volume is not part of the stability testing for brodalumab drub product at the long term, accelerated or stressed storage conditions. The sponsor concludes that the syringe functionality upon the 5° C is confirmed by the breakloose and extrusion force testing. The breakloose and extrusion forces for the 1.0 mL PFS have remained consistent through 48 months of storage at the recommended temperature and the 2.25 mL PFS for up to 12 months. They conclude that since no sterility, CCI or potency failures have been observed, and the breakloose and extrusion forces for the 1.0 mL prefilled syringe have remained consistent throughout 48 months of storage at 5°C, it can be inferred that no changes in the deliverable volume would be expected over the shelf life of the product. The deliverable volume is tested at release by real-time fill weigh testing.

There is also an optional short-term storage at room temperature (20° to 25 C) for no more than 2 weeks after removal from storage at 5°C.[Storage at 5 °C for 46 months and either 25°C or 30°C for 2 months]. The Breakloose and Extrusion for the 2 weeks at 25 to 30 °C all were well below $^{(b)(4)}N$.

Unlike a pen injector system where the user is relying on the spring mechanism to deliver the dose to the patient, the user would be able to visualize the amount of medication in the syringe and inject the entire 1.5 mL dose. If the syringe did not contain the required dose it would be visually apparent.

5. Risk Management

Risks to Health (Harm)	Control
Infection	Device design (dimensions required that prevent rolling off table, needle shield)
	Packaging Design (blister tray, keep needle shield in place and needle protected)
	IFU (proper storage condition requirements, do not use if dropped, cracked, broken, missing needle shield, use proper aseptic techniques, proper disposal techniques, use of sharps disposal container)
	Primary and secondary labeling (include storage requirements, single use only) HFE/UE testing
Immunogenic Response	Device design
	Packaging Design (protect from light)
	IFU (check expiry date, proper storage condition requirements, do not use if drug is discolored or contains lumps, flakes or colored particles, do not warm using heat source)
	Primary and secondary labeling (include expiry date, include storage requirements, protect from light, label does not block view of product or device) HFF/UF testing
Child Product Exposure	The secondary label and the IFU shall instruct the user to keep the PFS system out of the sight and reach of children

Highest Severity Potential Harms and Existing Controls for Brodalumab 1 mL Long and 2.25 mL Syringes

Design Validation

Design validation testing was conducted with production equivalent devices, labeling and packaging with the intended user population. Design validation consisted of an HFE/UE. A Summative Study to validate that the device is safe and effective for the intended user population. All injections were performed with a sterile solution that mimics the drug product and injected into a skin pad to simulate a subcutaneous injection. Based on the successful completion of the HFE/UE summative study, the 2.25 mL syringe is determined to be a validated design that meets all the intended user needs and provides evidence of safe and effective use of the system by the intended user population.

Intended User Population
Patients, Caregivers and Healthcare Providers
Device Uses and Use Environments
Intended for subcutaneous administration of brodalumab.
Administered at room temperature as described in the IFU
Dose administration should be performed in an environment with minimal distractions
Device-User Interface
Interaction with the device as a "closed-loop system" was analyzed to understand user
perceptions and assumptions, specifically how users handled packaging, labeling features on the
device such as device plunger, needle shield, syringe barrel and disposal.
The packaging was designed so that users would encounter the IFU before removing the PFS for
use, thus encouraging the user to review the instructions before beginning the injections.
 Moderator-trained participants received moderator-assisted walk-though of the IFU to
ensure they understand the drug administration procedure. After training to perform device
administration tasks, the moderator-trained participants were asked to wait 60 minutes, to
introduce a realistic amount of learning decay.
 Self-trained participants were asked to read the IFU on their own. Tasks did not
commence until they had confirmed verbally to the moderator that they were comfortable
with the tasks required of them.

Known Use Problems

The device, a PFS, is a relatively simple device and does not have a large variety of potential use errors.

- Failure to verify that the PFS is appropriate to use (checking expiration date)
- Failure to deliver a full dose
- Inadvertent needle stick injuries

Human Factors Engineering /Usability Engineering Studies for the PFS

Type of Study	Number of Participants	User Training	Key Learnings
October 2014 Human Factors Engineering Formative Study #1.	58 (35 patients, 11 caregivers and 12 healthcare providers.)	Self-Trained.	"Take 2" intro and "check your prescription" reminder messages were incorporated into the next versions of the IFU.
February 2015 Human Factors Engineering Summative Study	322 (128 patients, 130 caregivers, 64 healthcare providers)	Self-Trained and Moderator- Trained	Product is safe and effective from a usability perspective.

Formative Study Sample of Participants by Brodalumab PFS Presentation

User Group	Participant Type	1 mL Long Syringe w/ 1.0 mL Fill (1 injection)	1 mL Long Syringe w/ 0.75 mL Fill (2 injections)	2.25 mL Syringe w/ 1.5 mL Fill (1 injection)	Total
1	Patients	12	12	11	35
2	Caregivers	3	4	4	11
3	HCPs	4	4	4	12
	Total	19	20	19	58

Note: This formative study included both the 1mL Long and 2.25 mL syringe configurations. All conclusive findings relative to the 2.25 mL with 1.5 mL fill volume are included in this Device Design Validation 2.25 mL Syringe section. All conclusive findings relative to the 1 mL Long with 0.75 & 1.0 fill volumes are listed in the (Device Design Validation [1 mL Long Syringe]) section.

Г

#	Essential Steps for PFS Use	Study Technique	Success Criteria
1	Remove device from packaging	Participants will be observed if they can remove the PFS from the packaging.	Observation Participants must be able to remove PFS from package.
2	Remove needle cover	Participants will be observed if they can remove the needle cover.	Observation Participant must be able to completely remove the needle cover prior to performing the injection.
3	Place injection needle on injection site surface and pierce the skin	Participants will be observed whether they can pierce the needle at the injection site	Observation Participants must pierce the skin at the injection site.
4	Depress the syringe plunger rod to empty the entire drug product	Participants will be observed whether they push the plunger rod until the injection is complete.	Observation Participant must push the plunger rod until the injection is complete (visual confirmation of empty syringe by Moderator).
5	Remove device from injection site without needle-stick injury	Participants will be observed whether they can remove the needle from the injection site.	Observation Participant must pull the needle out of the skin.
6	Dispose of device without needle-stick injury	Participants will be observed whether they properly dispose of the used prefilled syringe.	Observation Participant must dispose of the used prefilled syringe and needle cover into sharps container.

Essential Steps for Brodalumab PFS

1

Summative Study Sample Breakdown of Participant by Brodalumab Condition

User Group	Participant Type	1 mL Long Syringe with 1.0 mL Fill (standard IFU)	2.25 mL Syringe with 1.5 mL Fill (standard IFU)	1 mL Long Syringe with 1.0 mL Fill (dosing IFU)	1 mL Long Syringe with 0.75 mL Fill (dosing IFU)	Total
1	HCPs	16	16	16	16	64
2	Patients	32	32	32	32	128
3	Caregivers	32	32	32	34	130
	Total	80	80	80	82	322

Note: This summative study included both the 1 mL Long and 2.25 mL syringe configurations. The 1 mL Long syringe with 1 mL fill volume had both (standard and dosing) IFU's, the 1 mL Long syringe with 0.75 fill volume had a (dosing) IFU; and the 2.25 mL syringe with 1.5 mL fill volume had a (standard) IFU. All conclusive findings relative to the 2.25 mL syringe with 1.5 mL fill volume is included below in this Device Design Validation 2.25 mL Syringe section. All conclusive findings relative to the 1 mL Long syringe with 1.0 & 0.75 mL fill volumes are listed in the (Device Design Validation [1 mL Long Syringe]) section.

Steps for brodalumab PFS	HFE Summative Results	Root Cause and Further Clarification
1. Remove device from packaging	100% success rate	N/A
2. Remove needle cover	98% success rate	Two (2) moderator-trained patients lost medication prior to administering the injection as the result of the plunger rod pushing down on the table top during needle cover removal.
3. Place injection needle on injection site surface and pierce the skin	100% success rate	N/A
4. Depress the syringe plunger rod to empty the entire drug product	99% success rate	One (1) moderator-trained patient did not push the plunger rod at all upon needle Insertion.
5. Remove device from injection site without needle-stick injury	100% success rate	N/A
 Dispose of device without needle-stick injury 	100% success rate	N/A

2.25 mL Syringe with	n 1.5 mL Fill Volume	(Standard IFU) Observations
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3 Pages have been Withheld in Full as Draft Labeling Immediately Following this Page.

Reviewer Comment:

Amgen incorporated the recommendations from the HFE/UE formative study, made iterative changes, and then validated the effectiveness of these changes through the summative study to ensure there were improvements to the overall design that reduced or eliminated potential errors. Based on the successful completion of these validation activities, it is concluded that the PFS is considered to be a validated design that meets all the intended user needs and provides evidence of safe and effective use by the intended user population. The methods and results described in the preceding sections support this conclusion. Any residual risk that remains after the validation testing would not be further reduced by modifications of design of the user interface (e.g., the IFUs) and is outweighed by the benefits that may be derived from use of the device and system per the overall favorable clinical benefit risk assessment in Module 2.5 (Clinical Overview).

The Instructions for Use was reviewed and were shown to be clear and concise. The pre-filled syringe does not contain an active or passive needle safety device, making it a simple device to use for patients and caregivers. The injection of medication in a pre-filled syringe is a basic task for a healthcare provider.

(b) (4)

6. Information Request

1. An information request was sent to the sponsor on March 8, 2016 and that request was sent tc^{(b) (4)} and a response was received on March 11, 2016.

^{(b) (4)} has provided an ISO 10	993 compliance statement for the	^{(b) (4)} 2.25 mL with 27g ½ inch needle.		
The applicable test article on the compliance statement is product code (b) (4)				
^{(b) (4)} 2.25ML27G		^{(b) (4)} glass syringe		
with attached needle and	^{(b) (4)} shield covered with	^{(b) (4)} rigid shield). I am unable to		
locate the needed information in the master file that was provided				

Please provide the following test reports: cytotoxicity, Sensitization, intracutaneous reactivity, acute systemic toxicity and hemocompatibility for the ^{(b) (4)} 2.25 mL with 27g ½ inch needle.

Sponsor response:

(b) (4) (b) (4) (b) (4)	2.25 mL Syringe Barrel with 27	Gauge 1/2 IN Needle and Rigid Needle
Shield (RNS) components (configura	ation referenced within the	^{(b) (4)} LOA) was assessed and meets the
established criteria for preclinical tox	icological safety evaluation. Tes	t selection and protocol designs were
performed in accordance with ISO 1	0993-1.	
		(b) (4)

All test report were provided by $\binom{b}{4}$ and were sent to the Device MAF.

 Table 1: Summary of the Biocompatibility Test Reports and associated Attachment Reference for the

 (b) (4)
 2.25 mL with 27g ½ inch needle

Biocompatibility Test Report Attachment Number Cytotoxicity Attachment 1 Sensitization Attachment 2 Intracutaneous Reactivity Attachment 3 Acute Systemic Toxicity Attachment 4 Hemocompatibility Attachment 5

This response is acceptable

- An information request was sent to the sponsor on April 7, 2016 and response was received on April 14, 2016,
 - In the Device design verification-2.25 mL Syringe [3.2.P.7] it states that an additional testing/assessment was done. The PFS was verified via a tolerance analysis to have a needle insertion depth of Provide test reports of verifying the needle depth of ^{(b) (4)}mm.

Sponsor response:

This response is acceptable.

3. In the stability data that was provided 3.2.P.8.3 stability information was provided for the recommended, accelerated and stressed conditions. Provide the location of the test results for the deliverable volume at the ^(b)₍₄₎month time period.

Sponsor Response:	
	(b) (4)

(b) (4)

An information request was sent to the sponsor on June14, 2016 and response was received on June 17, 2016.

4. In BLA 761032, I could not locate performance testing for the stainless steel staked needle used with the glass syringe for the device constituent part of the combination product.

(b) (4)

Please provide summary test results for the following:

- a. Needle shield removal force
- b. Needle pull out force
- c. Levels lubricant
- d. Levels adhesive used to fix needle inside the glass syringe

Sponsor Response:

Digital Signature Concurrence Table			
Reviewer Sign-Off	Digitally signed by Janice L. Ferguson, RN, CRNI DN: cn=Janice L. Ferguson, RN, CRNI, o=FDA, ou=CDRH, email=janice.ferguson@fda.hhs.gov, c=US Date: 2016.06.23 11:44:11 -04'00'		
Branch Chief Sign-Off	Alan M. Stevens -S DN: (-US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=130 0189211, (n=Alan M. Stevens -S Date: 2016.06.23 14:05:51 -04'00'		

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/s/

STROTHER D DIXON 06/28/2016
Department of Health and Human Services Public Health Service Food and Drug Administration Center for Drug Evaluation and Research Office of Surveillance and Epidemiology (OSE) Office of Pharmacovigilance and Epidemiology (OPE)

Epidemiology: Review of Clinical Trial Data

Date:	June 27, 2016
Reviewer(s):	Andrew D. Mosholder, MD, MPH, Medical Officer Division of Epidemiology I
Team Leader	Sukhminder K. Sandhu, PhD, MPH, MS, Team Lead Division of Epidemiology I
Division Director	Simone P Pinheiro, ScD MSc, Acting Deputy Director Division of Epidemiology 1
Subject	Risk of serious infections with brodalumab
Drug Name(s):	Brodalumab
Application Type/Number:	BLA 761032
Applicant/sponsor:	AstraZeneca
OSE RCM #:	RCM 2016-1450

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EXECUTIVE SUMMARY

The purpose of this review is for the Division of Epidemiology I (DEPI-I) to evaluate data on the occurrence of serious infections in brodalumab clinical trials, and to summarize available information on serious infections in psoriasis clinical trials with other biologics, to assist the Division of Dermatology and Dental Products (DDDP) in determining regulatory action on the pending brodalumab biologics license application (BLA). Brodalumab is a monoclonal antibody against interleukin 17 (IL-17) receptor A. The brodalumab BLA is under review with a proposed indication of moderate to severe plaque psoriasis in adult candidates for systemic therapy or phototherapy. In early 2014, safety monitoring identified suicidal ideation and behavior (SIB) as a safety concern in the brodalumab clinical trials, which eventually led Amgen to discontinue all brodalumab trials; thus, no additional clinical trial data are forthcoming.

Increased susceptibility to infections is regarded as a class effect of psoriasis biologics due to their immunosuppressant effects, and is a labeled risk for all such products. In 12-week placebo controlled trials, and 52-week ustekinumab controlled trials, comparisons of serious infection rates between brodalumab and controls involve very sparse data for the comparison groups, and are not informative. Comparing serious infection rates (i.e., serious adverse events involving infections) among brodalumab-treated psoriasis patients to those seen with other biologics, brodalumab's rate of 1.2 serious infections per 100 person-years of exposure was not markedly higher than that for other products, and was very close to the rate reported in the sponsor's systematic review (also 1.2 per 100 person-years). There were no cases of active tuberculosis reported in brodalumab trials, but to the extent that prospective subjects were screened for active/latent tuberculosis, the absence of cases in brodalumab trials should not be interpreted as evidence that brodalumab does not share this risk as seen with other psoriasis biologics. Apremilast had the second lowest rate of serious infections among psoriasis products. It may in fact be regarded as a "negative control" since it is not primarily an immunosuppressant and has no labeling regarding infection risk. The fact that it did not separate more clearly from the other products in this comparison illustrates the limitations of the analysis. First, use of external or historical comparisons is generally not as valid as internal controls. Data from different development programs may be subject to heterogeneity in patient characteristics, follow-up methods, and ascertainment of infections. The results reflect only a crude pooling of data across trials and products, rather than a patient or trial level meta-analysis, and do not take into account potential differences in confounders across programs.

In sum, the rate of serious infections observed with brodalumab treatment was similar to rates for the other psoriasis biologics. However, a causal relationship of brodalumab therapy to infection risk may be presumed, as a property shared with other immunosuppressive therapies for psoriasis.

Labeling as proposed by the sponsor regarding the risk of infections similar to other biologics, including tuberculosis, will be appropriate if brodalumab is marketed. Also, if brodalumab is approved, there is precedent for assessing infections as part of post-marketing requirement studies of malignancies for psoriasis biologics.

1 INTRODUCTION

1.1 BACKGROUND

The purpose of this review is to evaluate serious infections in clinical trial data for brodalumab, and to examine available data on serious infections among psoriasis patients in clinical trials of other biologics. The Division of Dermatology and Dental Products (DDDP) consulted DEPI-I as part of their review of BLA 761032 for brodalumab in the treatment of moderate to severe plaque psoriasis in adults. Since an inordinate number of suicides and MACE occurred in brodalumab trials relative to other psoriasis biologics, assessment of a different safety outcome across products may provide insights regarding the comparability of the brodalumab cohort to cohorts in other psoriasis development programs. Brodalumab is a human monoclonal antibody that binds to the interleukin-17 (IL-17) receptor A, thus blocking the pro-inflammatory effects of the interleukins IL-17A, IL-

Serious infection risk for brodalumab DEPI-I review

17C, IL-17F, IL-17A/F heterodimer, and IL-25. This is thought to be brodalumab' s mechanism of action in psoriasis.

Susceptibility to opportunistic and serious infections is a recognized risk from immunosuppressive therapies which are used for psoriasis (van Dartel et al. 2012, Galloway et al. 2011). Biologics approved for psoriasis have labeling (either in boxed warnings or in Warnings and Precautions) describing the risk of infection, and advising that patients be tested for latent tuberculosis prior to initiating therapy. An exception is apremilast, a small molecule phosphodiesterase 4 inhibitor with a poorly understood mechanism of action in psoriasis; it has no labeling regarding immunosuppression or increased risk of infection.

The Division of Dermatology and Dental Products requested an evaluation of the rate of serious infections in the brodalumab psoriasis trials, and a comparison to rates of serious infections in trials of other products indicated for psoriasis. This review is in response to that request.

1.2 REGULATORY HISTORY OF BRODALUMAB

- August 27, 2009: Amgen submits an Investigational New Drug (IND) Application for brodalumab (formerly known as AMG 827).
- February 6, 2014: Amgen issues a Dear Investigator letter describing suicidal adverse events in brodalumab clinical trials.
- May 13, 2015: FDA meets with Amgen to discuss the suicidality signal, and in response, Amgen decides not to submit the brodalumab BLA, and discontinues all subjects from ongoing brodalumab clinical trials.
- August 12, 2015: Amgen transfers brodalumab to co-developer AstraZeneca.
- October 21, 2015: FDA and AstraZeneca hold a pre-BLA meeting.
- November 16, 2015: AstraZeneca submits BLA 761032 for brodalumab in the treatment of moderate to severe plaque psoriasis, in adults who are candidates for systemic therapy or phototherapy.
- March 6, 2016: AstraZeneca completes the 120 day safety update to the brodalumab BLA.
- March 22, 2016: DEPI-I review of suicide risk.
- April 1, 2016: AstraZeneca notifies FDA it will transfer brodalumab to Valeant Pharmaceuticals.
- June 8, 2016: DEPI-I review of major adverse cardiovascular events.

1.3 Sponsor's Proposed Labeling

The following is the sponsor's proposed labeling regarding infections, for the "Highlights" label section.

•Infections: Serious infections have occurred. (b) (4) . If a serious infection develops, discontinue TRADENAME until the infection resolves. (5.3)

•Tuberculosis (TB): Evaluate patients for TB infection prior to initiating treatment with TRADENAME.

This is the sponsor's proposed labeling for the Warnings and Precautions section.

5.3 Infections

TRADENAME may increase the risk of infections. (b) (4) [see Adverse Reactions (6.1)]. 5.4 ^{(b) (4)}

Evaluate patients for tuberculosis (TB) infection prior to initiating treatment with TRADENAME. Do not administer TRADENAME to patients with active TB infection. Initiate treatment for latent TB prior to administering TRADENAME.

Consider anti-TB therapy prior to initiation of TRADENAME in patients with a past history of latent or active TB in whom an adequate course of treatment cannot be confirmed.

2 MATERIALS REVIEWED

- Brodalumab BLA and 120-day safety update
- Clinical trial data from recent regulatory submissions for other products indicated for psoriasis
- Related literature publications

3 REVIEW RESULTS

3.1 SERIOUS INFECTIONS IN BRODALUMAB PSORIASIS CLINICAL TRIALS

3.1.1 Overview of clinical development program

Table 1 summarizes the overall exposure to brodalumab in psoriasis clinical trials, which are the focus of this review. Subjects were typically seen one final time for an end-of-treatment follow-up visit after their last dose; the total exposure time shown for psoriasis subjects includes an average of 6-7 weeks of follow-up time after the last dose of brodalumab. For the indication of psoriasis, the sponsor conducted trials of different designs. Phase III trial 102 (N=661) included a 12-week placebo control period, and a placebo-controlled withdrawal period after the initial 12 weeks. Phase III trials 103 (N=1861) and 104 (N=1881) included both a 12-week placebo- and ustekinumab-controlled period, and a 52 week ustekinumab-controlled period. The sponsor pooled safety data for analysis according to these designs and treatment periods.

Dataset	Ν	Exposure to active treatment in patient- years	Exposure in patient- years including all follow-up time
Brodalumab, psoriasis trials only (including 4 month safety update)	4,464	8,655.0	9,173.9

Table 1. Overall brodalumab exposure in psoriasis clinical trials (BLA Day 120 Safety Update, 06 March 2016)

Among 3066 psoriasis subjects in placebo-controlled trials (see below), approximately 69% were male, 91% were white, and 57% were 40 to 64 years old.

3.1.2 Incidence of serious infection events in brodalumab psoriasis trials—12-week placebo-controlled period

Table 2 summarizes the rates of serious infections for all brodalumab subjects in psoriasis trials. The left columns show pooled data on the numbers of patients with serious adverse events involving infections in the initial 12-week double-blind placebo-controlled periods of the psoriasis trials. The middle columns show the pooled rates individually for ustekinumab and brodalumab during the 52-week active controlled periods of the trials, and the right hand column shows the pooled data from all psoriasis patients treated with brodalumab.

Rates (shown per 100 person-years) were fairly similar, though of course ustekinumab also has immunosuppressive properties.

Dataset	12-week	12-week placebo-controlled trials**			52 week active controlled trials***		
Treatment group	Placebo	Ustekinumab	Brodalumab	Ustekinumab	Ustekinumab (includes follow- up person time)		
N	879	613	3066	613	4019	4464	
Person-years	n/a	n/a	n/a	504	3547.7	9174	
Serious infections	2 (0.23%)	2 (0.33%)	14 (0.46%)	5	50	109†	
Serious infections /100 person-years	n/a	n/a	n/a	1.0	1.4	1.2	

Table 2. Serious	infections in	brodalumab	clinical trials	by the indicated	pool of trial data*
14010 2. 0011040		010441411140	ennear enals	, of the maleated	poor or tildi data

Sources: *Different pools have different numbers of subjects and person-years.) **BLA Summary of Clinical Safety ***Table 14-6.33.1.1, BLA Integrated Summary of Safety ****BLA 4 month safety update

[†]includes 1 coccidioidomycosis and 1 cryptococcal meningitis

3.2 RATES OF SERIOUS INFECTIONS IN CLINICAL TRIALS OF OTHER PSORIASIS TREATMENTS

3.2.1 Data from Sponsor's Systematic Review of Psoriasis Clinical Trials

Exponent Inc., consultants to Amgen, conducted a systematic review of a variety of adverse events in phase III and phase IV clinical trials of adult patients with psoriasis and/or psoriatic arthritis treated with biologic agents, using literature and publicly available data. Results of the systematic review were submitted as part of the Amgen pre-BLA meeting package. The phase III/IV clinical trial data reviewed included open-label extensions of phase III trials, phase II/III trials, and trials of unspecified phase with at least 100 subjects. The studies reviewed included patients treated with the following agents: adalimumab, apremilast, certolizumab pegol, etanercept, golimumab, infliximab, secukinumab, and ustekinumab. Public domain data for ixekizumab or brodalumab were not available, so those agents were not included. Presumably apremilast was excluded from the analysis limited to biologics, though that was not stated explicitly.

Table 4 presents the incidence of serious infections in psoriasis patients treated with the aforementioned biologics in phase III or IV clinical trials, from Exponent, Inc.'s systematic review. The rate of serious infections in brodalumab psoriasis trials (1.2 per 100 person-years) is consistent with the rate from the sponsor's systematic review (also 1.2 per 100 person-years).

Table 4. Serious infections in psoriasis patients treated in Phase III/IV trials*, Sponsor's systematic review								
Total Studies	Total Serious Infections	Total Person- Years	Serious Infections per 100 Person- Years	95% Confidence Interval				
25	248	19,521.8	1.184	1.081-1.294				

*Biologics included: adalimumab, certolizumab pegol, etanercept, golimumab, infliximab, secukinumab, and ustekinumab

3.2.2 Data from Regulatory Submissions

To provide a comparison of data on serious infections for brodalumab to trials of other products in patients with psoriasis, data on serious infections were abstracted from other regulatory submissions for drugs and biologics

Serious infection risk for brodalumab DEPI-I review

in the treatment of psoriasis, from the sources noted in Table 5. All data are from psoriasis trials. Only the data for the product under development are shown, as the placebo and active comparator groups had limited sample sizes. Briakinumab has never been marketed.

Table	Table 5. Rates of Serious Infections with Exposure to Specific Products in Psoriasis Trials							
Product	Patient N	Exposure PY	Serious infections N	Active TB N	Fatal infections N	Serious infections/ 100 PY	Active TB/ 100 PY	
Brodalumab (with 120 Day Safety Update)	4,464	9174	109	n/a	0	1.19	n/a	
Adalimumab (1)	1,468	4,069	53	6	0	1.30	0.15	
Apremilast (2)	1,184	1,422	13	0	0	0.91	0	
Briakinumab (3)	2,520	4,704	41	n/a	0	0.87	n/a	
Etanercept (4)	1,160	2,052	26	0	0	1.27	0	
Infliximab (5)	1,654	1260	23*	2	1	1.83	0.16	
lxekizumab (6)	4,209	6,480	87	n/a	0	1.34	n/a	
Secukinumab (7)	3,430	2,725	40	0	0**	1.47	0	
Ustekinumab (8)	3,117	6,791	75	0	3	1.10	0	

Summary data across products are subject to heterogeneity in patient characteristics, follow-up methods, & ascertainment of events. *Numerator is number of patients, not number of infections. DEPI assumes for other products the numerators is number of infections. **A death from disseminated aspergillosis occurred a year post-treatment. Data sources: (1) Clinical Study Report MO3-658; (2) 4msu; (3) Langley et al. JEADV 2013, 27, 1252–1261; (4) Integrated Summary of Safety for Long-Term Exposure, 12-13-2006; (5) SCS; (6) 4msu and SCS; (7) SCS; (8) SCS Year 4 Update

PY patient-years, 4msu 4 month safety update, SCS Summary of Clinical Safety

The following graph displays the incidence rates and 95% confidence intervals for these rates (as shown above) of serious infections in psoriasis clinical trials with the indicated products. The confidence intervals were calculated in Stata 11. The confidence intervals overlap, and the width of the confidence intervals indicates the lack of statistical precision for these estimates. Brodalumab' s rate was not was similar to the rates for the other products. Apremilast, which is not labeled for immunosuppression, had the second lowest rate; also, the sponsor for apremilast was the only one to adjudicate events reported as serious infections.



Data sources: (1) Clinical Study Report MO3-658; (2) 4msu; (3) Langley et al. JEADV 2013, 27, 1252–1261; (4) Integrated Summary of Safety for Long-Term Exposure, 12-13-2006; (5) SCS; (6) 4msu and SCS; (7) SCS; (8) SCS Year 4 Update

4 DISCUSSION

There are important limitations to the examination of serious infection rates across trials and development programs. First, use of external or historical comparisons is generally not as valid as internal controls. Data from different development programs may be subject to heterogeneity in patient characteristics, follow-up methods, and ascertainment of infections. Only one sponsor adjudicated potential cases of serious infections. The data shown represent a crude pooling of data across trials and products, rather than a patient or trial level meta-analysis, and do not take into account potential confounders. For pooling data with person time from different durations of treatment in this way to be valid, the risk should remain constant over different durations of exposure. However, in the absence of evidence, this is an assumption.

Fatal infections were a relatively small proportion of the total number of infections across products, and there were no deaths from infections in brodalumab trials. Also, there were no cases of active tuberculosis reported in brodalumab trials, but to the extent that prospective subjects were screened for active/latent tuberculosis, the absence of cases in brodalumab trials should not be interpreted as evidence that brodalumab does not share this risk seen with other psoriasis biologics.

Apremilast had the second lowest rate of serious infections. It may in fact be regarded as a "negative control" since it is not primarily an immunosuppressant and has no labeling regarding infection risk. The fact that it did not separate more clearly from the other products in this comparison illustrates the limitations of the analysis. In addition, the apremilast rate was the only one calculated after adjudication of cases, so the rate "as reported" may have been even higher.

5 CONCLUSIONS

The rate of serious infections observed with brodalumab treatment was similar to rates for the other psoriasis biologics. However, a causal relationship of brodalumab therapy to infection risk may be presumed, as a property shared with other immunosuppressive therapies for psoriasis.

6 RECOMMENDATIONS

Serious infection risk for brodalumab DEPI-I review

- Labeling as proposed by the sponsor regarding the risk of infections similar to other biologics, including tuberculosis, is appropriate if brodalumab is marketed.
- If brodalumab is approved, there is precedent for assessing infections as part of post-marketing requirement studies of malignancies for psoriasis biologics.

CC: Bui-Nguyen T/ OSE Sandhu S, Taylor L, Mosholder A, Wang C, Calloway P, Pinheiro S/ DEPI I Gary Chiang, David Kettl / DDDP Jasminder Kumar, Jamie Wilkins Parker / DRISK Ida-Lina Diak, Jessica Weintraub / DPV

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

Epidemiology: Review of Clinical Trial Data

Date:	June 8, 2016
Reviewer(s):	Andrew D. Mosholder, MD, MPH, Medical Officer Division of Epidemiology I
Team Leader	Sukhminder K. Sandhu, PhD, MPH, MS, Team Lead Division of Epidemiology I
Division Director	Simone P Pinheiro, ScD MSc, Associate Director Division of Epidemiology 1
Subject	Risk of major adverse cardiovascular events (MACE) in patients treated with brodalumab
Drug Name(s):	Brodalumab
Application Type/Number:	BLA 761032
Applicant/sponsor:	AstraZeneca
OSE RCM #:	2015-686

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EXECUTIVE SUMMARY

The purpose of this review is for the Division of Epidemiology I (DEPI-I) to evaluate data on major adverse cardiovascular events (MACE) in brodalumab clinical trials, and to summarize available information on MACE in psoriasis clinical trials with other biologics, to assist the Division of Dermatology and Dental Products (DDDP) in determining regulatory action on the pending brodalumab biologics license application (BLA). Brodalumab is a monoclonal antibody against the interleukin 17 (IL-17) receptor A. The brodalumab BLA is under review for the indication of moderate to severe plaque psoriasis in adults who are candidates for systemic therapy or phototherapy. In early 2014, safety monitoring identified suicidal ideation and behavior (SIB) as a safety concern in the brodalumab clinical trials, which eventually led Amgen to discontinue all brodalumab trials; thus, there will be no additional clinical trial data on MACE forthcoming.

In 12-week placebo controlled trials, and 52-week ustekinumab controlled trials, comparisons of event rates involve very sparse data for the comparison groups, and are not informative. Comparing MACE rates among brodalumab-treated psoriasis patients to those seen with other biologics, brodalumab had the numerically highest MACE rate in clinical trials (6.5 per 1000 person years), higher than the rate of 4.3 per 1000 person years found in the sponsor's systematic review of MACE in psoriasis biologic trials.

There are important limitations to these data. First, use of external or historical comparisons is generally not as valid as internal controls. Data from different development programs may be subject to heterogeneity in patient characteristics, follow-up methods, and ascertainment of MACE. The results reflect only a crude pooling of data across trials and products, rather than a patient or trial level meta-analysis, and do not take into account potential differences in confounders across programs.

Further evaluation of the risk of MACE with brodalumab is recommended, given the plausible association of MACE with elevated serum IL-17 levels resulting from brodalumab treatment.

- A cardiovascular outcome randomized clinical trial would be challenging but would provide the highest quality data.
- If brodalumab is approved, there are reliable observational techniques for studying MACE which could be applied post-marketing—but only if the market uptake of brodalumab is sufficient to provide a large enough sample.
- Analysis of the existing clinical trial data on IL-17 levels among brodalumab-treated subjects could provide insights into the possible association with MACE, if it were to be found that subjects with greater IL-17 increases had higher rates of MACE events.

1 INTRODUCTION

1.1 BACKGROUND

The purpose of this review is to evaluate MACE, defined as myocardial infarction (MI), stroke, or cardiovascular death, in clinical trial data for brodalumab, and to survey available data on MACE among psoriasis patients in clinical trials of other biologics. The Division of Dermatology and Dental Products (DDDP) consulted DEPI-I as part of their review of BLA 761032 for brodalumab in the treatment of moderate to severe plaque psoriasis in adults. Brodalumab is a human monoclonal antibody that binds to the interleukin-17 (IL-17) receptor A, thus blocking the pro-inflammatory effects of the interleukins IL-17A, IL-17C, IL-17F, IL-17A/F heterodimer, and IL-25. This is thought to be brodalumab's mechanism of action in psoriasis.

There is evidence that psoriasis patients have a higher rate of MACE than the general population. A metaanalysis of six cohort studies found a combined relative risk for MI with psoriasis versus the general population of 1.25 (95% CI 1.03, 1.52) (Horreau et al. 2013). Risk factors such as hyperlipidemia, hypertension, smoking and obesity have been shown to have increased prevalence among psoriasis patients (Wakkee et al. 2006). Furthermore, a recent Spanish study suggested that cardiovascular (CV) risk factors tend to be under-recognized in psoriasis patients; the authors advocated screening of psoriasis patients for CV risk factors by dermatologists (Cea-Calvo et al., 2016). However, there is evidence that the CV risk associated with psoriasis is not entirely accounted for by a higher prevalence of risk factors. A study in the UK General Practice Research Database found that psoriasis patients had a higher risk of MI even after adjusting for customary cardiovascular (CV) risk factors (Gelfand et al. 2006). Similarly, a later study in the same database found that psoriasis was associated with higher CV mortality, also independent of usual CV risk factors (Mehta et al. 2010).

It has been proposed that IL-17 has a pathogenic role not only in psoriasis but also in atherosclerosis, and that this may be one explanation for the fact that psoriasis is a risk factor for cardiovascular disease; speculatively, agents active against IL-17 may convey cardiovascular benefits for psoriasis patients (Golden et al. 2013, Su et al. 2013). However, data submitted with the BLA indicate that brodalumab treatment raises circulating IL-17A concentrations, which could mean that brodalumab treatment might accelerate atherosclerosis and thereby may increase the incidence of MACE.

With respect to cardiovascular events with other biologics in the treatment of psoriasis, it should be noted that the tumor necrosis factor (TNF) blockers etanercept, adalimumab, and infliximab, have been associated with heart failure; all carry labeling under Warnings and Precautions describing this association. There have also been concerns about the safety of MACE after ustekinumab, another biologic for psoriasis.

In this context, DDDP sent the following consult request to DEPI-I on April 7, 2016: "Provide assistance in evaluating the significance of Major Cardiovascular Adverse Events in the safety population of brodalumab. Compare the rate of MACE in brodalumab versus other biologics to determine the significance of the risks."

1.2 REGULATORY HISTORY

- August 27, 2009: Amgen submits an Investigational New Drug (IND) Application for brodalumab (formerly known as AMG 827).
- February 6, 2014: Amgen issues a Dear Investigator letter describing suicidal adverse events in brodalumab clinical trials.
- May 13, 2015: FDA meets with Amgen to discuss the suicidality signal, and in response, Amgen decides not to submit the brodalumab BLA, and discontinues all subjects from ongoing brodalumab clinical trials.
- August 12, 2015: Amgen transfers brodalumab to co-developer AstraZeneca.
- October 21, 2015: FDA and AstraZeneca hold a pre-BLA meeting.
- November 16, 2015: AstraZeneca submits BLA 761032 for brodalumab in the treatment of moderate to severe plaque psoriasis, in adults who are candidates for systemic therapy or phototherapy.
- March 6, 2016: AstraZeneca completes four month safety update for brodalumab BLA.
- April 1, 2016: AstraZeneca notifies FDA it will transfer brodalumab to Valeant Pharmaceuticals.

2 MATERIALS REVIEWED

- Brodalumab BLA, BLA 120-day safety update, and response to information request regarding MACE
- Clinical trial data from recent regulatory submissions for other products indicated for psoriasis

3 REVIEW RESULTS

3.1 INCIDENCE OF MACE IN BRODALUMAB CLINICAL TRIALS

3.1.1 Overview of clinical development program

Most brodalumab trials were for the indication of psoriasis, but other indications included psoriatic arthritis, rheumatoid arthritis, asthma, and Crohn's disease. Design characteristics of various Phase III trials included 12-week double blind comparisons to placebo and to ustekinumab, re-randomizations after 12 weeks, 52 weeks of treatment with ustekinumab as a comparator, and extended open label brodalumab treatment beyond 52 weeks. Specifically, Phase III trial 102 (N=661) included a 12-week placebo control period, and a placebo-controlled withdrawal period after the initial 12 weeks. Phase III trials 103 (N=1861) and 104 (N=1881) included both a 12-week placebo- and ustekinumab-controlled period, and a 52 week ustekinumab-controlled period. The sponsor pooled safety data for analysis according to these designs and treatment periods.

Table 1 summarizes the overall exposure to brodalumab in clinical trials. Subjects were typically seen one final time for an end-of-treatment follow-up visit after their last dose; the total exposure time shown for psoriasis subjects includes an average of 6-7 weeks of follow-up time after the last dose of brodalumab.

Dataset	Ν	Exposure to active treatment in patient- years	Exposure in patient- years including all follow-up time
Brodalumab, all trials (including 4 month safety update)	6,243	9,719.7	10,452
Brodalumab, psoriasis trials only (including 4 month safety update)	4,464	8,655.0	9,173.9

Table 1. Overall brodalumab exposure in clinical trials¹

Among psoriasis subjects, approximately 70% were male, 90% were white, and 57% were 40 to 64 years old.

3.1.2 Incidence of MACE events in brodalumab psoriasis trials

The sponsor adjudicated potential MACE events in Phase 3 psoriasis trials 20120102, 20120103, and 20120104, by convening a cardiovascular events committee, and defined MACE as CV death, MI, or stroke. Accordingly, the numerators presented below for Phase 3 psoriasis trials all represent adjudicated outcomes.

Table 2 summarizes the rates of adjudicated MACE for all brodalumab subjects in Phase 3 psoriasis trials, (source: BLA 4 month safety update and sponsor's response to MACE Information Request). Rates are per 1000 person-years, a conventional unit for incidence rates of MACE; confidence intervals were supplied by the sponsor or calculated by this reviewer in Stata 11.

In the 12-week placebo-controlled trial phase, there were only 3 MACE events, all occurring in patients on lowdose brodalumab. The totals are shown in the left hand columns in the table. On balance, the placebo-controlled trial data are two sparse to be of inferential value.

The middle columns show the comparison of events during the 52-week active controlled phase of the trials (source: Table 16 in the BLA 4 month safety update). The rate of MACE was numerically higher for brodalumab than ustekinumab, chiefly due to a roughly two-fold higher rate of MI, but the ustekinumab data are too limited to for a meaningful comparison.

¹ Source: Brodalumab BLA Day 120 Safety Update, 06 March 2016

The right hand columns show the rate of MACE for the entire psoriasis Phase 3 trial dataset, including all person-time beyond the 52-week active controlled phase. The rate was consistent whether follow-up person-time after active treatment was included or not, though slightly numerically higher with that follow-up time included. The rate was similar but somewhat higher than that for ustekinumab in the 52 week controlled trial phase.

	12-week placebo controlled			52 week activ	e controlled	All psoriasis Phase 3 brodalumab subjects		
	Placebo	Ustekinumab	Brodalumab	Ustekinumab	Brodalumab (includes follow-up person time)	Brodalumab (includes follow-up person time)	Brodalumab, exposed person time only	
Ν	842	613	2908	613	3828	4273	4273	
Person years (pyr)	-	-	-	511.0	3378.3	8365.2	7870.4	
MACE	0	0	3	2	24	54	40	
CV death	0	0	0	1	3	12	5	
MI	0	0	2	1	16	30	25	
Stroke	0	0	1	0	5	12	10	
MACE/1000 pyr (95% CI)	-	-	-	3.9 (0.5, 14.1)	7.1 (4.6, 10.6)	6.5 (4.8, 8.4)	5.1 (3.6, 6.9)	
CV death/1000 pyr (95% CI)	-	-	-	2.0 (0.05, 10.9)	0.9 (0.2, 2.6)	1.4 (0.7, 2.5)	0.6 (0.2, 1.5)	
MI/1000 pyr (95% CI)	-	-	-	2.0 (0.05, 10.9)	4.7 (2.7, 7.7)	3.6 (2.4, 5.1)	3.2 (2.1, 4.7)	
Stroke/1000 pyr (95% CI)	-	-	-	0 (0, 7.2)	1.5 (0.5, 3.5)	1.4 (0.7, 2.5)	1.3 (0.6, 2.3)	

Table 2. Rates of adjudicated MACE in brodalumab psoriasis trials

3.2 RATES OF MACE IN CLINICAL TRIALS OF OTHER PSORIASIS TREATMENTS

3.2.1 Data from Sponsor's Systematic Review of Psoriasis Clinical Trials

Exponent Inc., consultants to Amgen, conducted a systematic review of a variety of adverse events in phase III and phase IV clinical trials of adult patients with psoriasis and/or psoriatic arthritis treated with biologic agents, using literature and publicly available data. Results of the systematic review were submitted as part of the Amgen pre-BLA meeting package. The phase III/IV clinical trial data reviewed included open-label extensions of phase III trials, phase II/III trials, and trials of unspecified phase with at least 100 subjects. The studies reviewed included patients treated with the following agents: adalimumab, apremilast, certolizumab pegol, etanercept, golimumab, infliximab, secukinumab, and ustekinumab. Public domain data for ixekizumab or brodalumab were not available, so those agents were not included. Presumably apremilast was excluded from the analysis limited to biologics, though that was not stated explicitly.

Table 3 presents the incidence of MACE in psoriasis patients treated with the aforementioned biologics in phase III or IV clinical trials, from Exponent, Inc.'s systematic review.

Table 3. Incidence of MACE among subjects with psoriasis (including psoriasis with psoriatic arthritis) treated with biologics in phase III or IV clinical trials.

Adverse event	Total Studies	Total Events	Total Patient- Years	Events per 100 Patient- Years	95% Confidence Interval
MACE	10	51	11,933.0	0.427	0.318-0.562
Myocardial infarction	15	58	19,404.9	0.299	0.227-0.386
Stroke	11	19	18,004.8	0.106	0.064-0.165

Source: Exponent, Inc. report for Amgen, submitted with 5-13-15 pre-BLA meeting materials.

The Biologics included: adalimumab, certolizumab pegol, etanercept, golimumab, infliximab, secukinumab, and ustekinumab

estimated rate of MACE in these trials was lower than that observed with brodalumab; i.e., 4.3 per 1000 person years versus a roughly 50% higher rate of 6.5 per 1000 person years for brodalumab (Table 2). However, limitations to the comparisons of these data to the trial data for brodalumab (Table 2) include lack of details regarding patient characteristics, trial methods, and ascertainment of MACE.

In the original BLA submission, the sponsor noted results of their own systematic review of MACE in published studies of psoriasis treatments, stating:

The estimated MACE rate for the category of all psoriasis agents treatments (n=19498.5 subject-years) was 0.451 per 100 subject years (95% CI: 0.362, 0.556)

The submission did not provide details, but the rate estimate agreed with that from the Exponent, Inc. report.

3.2.2 Data from Regulatory Submissions

To provide a comparison of data for brodalumab to MACE previously observed in trials of patients with psoriasis, this reviewer surveyed data on MACE from other regulatory submissions for drugs and biologics in the treatment of psoriasis. From the sources noted in Table 4, the reviewer obtained event counts for MACE, with corresponding person-time of exposure and numbers of subjects. All data are from psoriasis trials. Only the data for the product under development are shown, as the placebo and active comparator groups had limited sample sizes. Briakinumab has never been marketed.

Psoriasis product	N	Exposure pyrs	MACE	CV death	MI	Stroke	MACE per 1000	CV death per	MI per 1000	Stroke per 1000	Adjudicated y/n?
							руі	pyr	יעץ	руі	
Brodalumab, Psoriasis Phase 3 trials only (4 mo su)	4,273	8365.2	54	12	30	12	6.46	1.43	3.59	1.43	у
Apremilast (1)	1,184	1,422	8	n/a	n/a	n/a	5.63	n/a	n/a	n/a	у
Briakinumab (2)	2,520	3,011	18	4	11	3	5.98	1.33	3.65	1.00	у
lxekizumab (3)	4,035	6,026.4	38	7	25	6	6.31	1.16	4.15	1.00	у
Secukinumab (4)	3,494	n/a	11*	1	5	6	3.6	0.3	1.6	2.0	n
Ustekinumab (5)	3,705	9,442	36	2	30	4	3.81	0.21	3.18	0.42	у

Table 4. Rates of major adverse cardiovascular events (MACE) with treatment by specific products in psoriasis clinical trials

Summary data across products are subject to heterogeneity in patient characteristics, follow-up methods, & ascertainment of events. Data sources: (1) 4 mo su; (2) EMA report; (3) 4 mo su; (4) MACE Information Request response; (5) MACE Information Request response

*Categories not mutually exclusive

pyr=patient-years, 4 mo su=4 month safety update

An analysis of MACE for adalimumab, etanercept, or infliximab could not be located

Numerically, brodalumab had the highest rate of MACE across products, and also the numerically highest rate of CV death, though other products had rates approaching those for brodalumab.

The following graph displays the incidence rates and 95% confidence intervals for MACE in psoriasis clinical trials with the indicated products. The confidence intervals for apremilast, briakinumab and ixekizumab were calculated by this reviewer in Stata 11, and the remainder were provided by the specific sponsor Estimated MACE incidence rates per 1000 person-years range from a low of 3.6 for secukinumab, to a high of 6.5 for brodalumab. The confidence intervals overlap, and the width of the confidence intervals indicates the lack of statistical precision for these estimates.



4 DISCUSSION

There are important limitations to the approach of examining MACE rates across trials and development programs. First, use of external or historical comparisons is generally not as valid as internal controls; however, the MACE data from controls in the brodalumab trials was too sparse to be useful. Data from different development programs may be subject to heterogeneity in patient characteristics, follow-up methods, and ascertainment of MACE. Most--but not all--sponsors adjudicated potential MACE cases. The data shown represent a crude pooling of data across trials and products, rather than a patient or trial level meta-analysis, and do not take into account potential confounders. For pooling data with person time from different durations of treatment in this way to be valid, the risk of MACE should remain constant over different durations of exposure. However, in the absence of evidence, this is an assumption.

Though ustekinumab had one of the lowest overall MACE rates in its psoriasis trials, there is some evidence that it may have a positive risk for MACE. In the controlled phase of the ustekinumab psoriasis trials, all 6 MACE events occurred with ustekinumab and none with controls. The sponsor's trial meta-analysis (source: Stelara MACE Safety Report, submitted September 3, 2014) showed the following:

"For the psoriasis indication, the RD point estimates are 0.152% (95% CI: -0.104%, 0.428%) and 0.199% (95% CI: 0.008%, 0.389%) for the exact method and modified MH methodologies respectively. The lower bound of the modified MH CI was >0, suggesting a small increase in risk."

The EMA's Rapporteurs' Day 80 Critical Assessment Report on briakinumab (dated December 10, 2010) regarded briakinumab to have a signal for MACE, with an event rate of 6.0 per 1000 person-years (i.e., slightly lower than brodalumab's). There was an imbalance in MACE events favoring placebo in the placebo-controlled trials. It is not clear whether this concern was the reason briakinumab was never marketed.

Ixekizumab was not regarded to have a signal for MACE, but it had the second highest rate of MACE in clinical trials, after brodalumab.

MACE risk for brodalumab DEPI-I review_final.doc

It may be asked why the limitations of the data presented herein would not also apply to the previous consult comparing suicides with brodalumab to other psoriasis biologics,² since the methods were similar. In fact, the aforementioned limitations do apply to that analysis as well. However, the imbalances in the number of events are considerably more disproportionate for the brodalumab suicide analysis. The MACE rates across products cover a less than two-fold range (from secukinumab with 3.6 per 1000 person-years, to brodalumab with 6.5 per 1000 person years). The rate of suicide in brodalumab trials was roughly three-fold higher than with other biologics and the number of completed suicides in brodalumab trials roughly equals or exceeds the number of suicides from all other psoriasis biologics combined.

Still, the rate of MACE need not be double or triple the expected rate to convey a clinically important risk. A meta-analysis of clinical trials of coxibs showed a relative risk versus placebo of 1.37 (1.14, 1.66) for major vascular events (CNT Collaboration, 2013). On the other hand, a clinical trial meta-analysis found that use of aspirin for cardioprotection in patients with vascular disease resulted in a relative risk of 0.69 (0.60-0.80) for nonfatal MI (Vandvik et al., 2012). Changes in MACE risk of 30-40% can be very clinically meaningful, but the current dataset for brodalumab cannot provide such precise risk estimates.

5 CONCLUSIONS

Rates of MACE were numerically higher in brodalumab psoriasis trials than in trials with other biologics in psoriasis patients. However, this comparison should be regarded as crude because of the caveats noted above, and the disproportion was much less for MACE than was the case in the previous review of suicide with psoriasis biologics. The brodalumab trials lacked adequate placebo or active control groups with which to make meaningful comparisons of MACE rates. While the trial data could be consistent with a clinically important increase in MACE with brodalumab, they are not conclusive.

6 **RECOMMENDATIONS**

Further evaluation of the risk of MACE with brodalumab is recommended, given the plausible association of MACE with elevated serum IL-17 levels resulting from brodalumab treatment.

- A cardiovascular outcome randomized clinical trial would provide the highest quality data, but such a trial would involve considerable time and effort.
- If brodalumab is approved, reliable observational techniques for studying MACE exist and could assess the association of brodalumab with MACE in the post-marketing environment—but only if the market uptake of brodalumab is sufficient to provide a sample, otherwise it could take years to accrue adequate numbers of users in observational databases.
- Analysis of the existing clinical trial data on IL-17 serum concentrations among brodalumab-treated subjects could provide insights into the possible association with MACE, if it were to be found that subjects with greater IL-17 increases had higher rates of MACE events.

CC: Bui-Nguyen T/ OSE Sandhu S, Taylor L, Mosholder A, Shih D, Wang C, Calloway P, Pinheiro S/ DEPI I Gary Chiang, David Kettl / DDDP Jasminder Kumar, Jamie Wilkins Parker / DRISK Ida-Lina Diak, Jessica Weintraub / DPV

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CONSULTATIVE REVIEW AND EVALUATION OF CLINICAL DATA CONSULT #11562

Consultant Reviewer: Consultation Requestor: Subject of Request: Date of Request: Date Received: Desired Completion Date: Jean Kim MD, MA, Medical Officer, OND-ODE1-DPP Strother D. Dixon, RPM, ODE III, DDDP BLA 761032 (Brodalumab) 12/2/2015 12/3/2015 6/13/2016

I. Background

Brodalumab (also known as AMG 827) is a monoclonal antibody that selectively targets the human interleukin-17 receptor (IL-17R) and antagonizes the IL-17 pathway. It binds with high affinity to human IL-17R and blocks the biological activity of IL-17A, IL-17C, IL-17F, IL-17A/F heterodimer, and IL-25. It is has been developed to treat moderate to severe plaque psoriasis. The proposed dosing regimen is 210 mg subcutaneously at weeks 0, 1, and 2, followed by 210 mg every 2 weeks (Q2W). On August 12, 2015, Amgen, an original co-sponsor of brodalumab, withdrew their sponsorship and transferred it to the sole sponsorship of AstraZeneca.

DDDP had requested consultation with DPP in March 2014 to seek advice regarding psychiatric adverse events in Phase 3 trials after several reports of suicidal ideation or behavior (SIB) were reported to the Agency. The consultative review was completed by Cara Alfaro, Pharm.D., in July 2014 and recommended safety changes such as administration of the Columbia Suicide Severity Rating Scale (C-SSRS), cutoff scores for the Patient Health Questionnaire-8 (PHQ-8) or Beck Depression Inventory (BDI) for both study entry and for safety monitoring during the study, additional exclusion criteria to screen out severe SIB cases, and a quantitative analysis of the comparative SIB signal between treatment and control groups. The sponsor agreed to add the C-SSRS to monitor for SIB (which changed some of the exclusion criteria mid-study, in May 2014); the recommendations were communicated to them in meetings before DPP's review was finalized. There was also a blinded, independent adjudication of all potential SIB events identified from a list of MedDRA terms, with subsequent classification using the Columbia-Classification Algorithm for Suicide Assessment (C-CASA).

The Division of Psychiatry Products (DPP) has been consulted again by DDDP to review the data from the BLA submitted by AstraZeneca on November 17, 2015, and to provide input on safety concerns about psychiatric adverse effects associated with brodalumab, such as suicidal ideation and behavior, and to clarify whether these events are a primary drug effect or reflect the background occurrence of these events in a patient population that has higher rates of depression and suicidal ideation and behavior.

II. Review of Clinical Data

A. Selection of Relevant Clinical Trials

The efficacy of brodalumab is supported primarily by 3 global pivotal, Phase 3 placebo-controlled studies (2012-0102, 2012-0103, and 2012-0104).

For the purposes of this review, I will examine these 3 trials because they are similar in design and enrolled a larger number of patients compared to other studies in this program. These trials all began with a 12-week placebo-controlled induction phase that will be the focus of this review. Subsequent to that phase of each study, patients were re-randomized to drug, placebo, or active control, rendering cross-treatment comparisons unreliable primarily because of loss of the randomized character of the treatment groups beyond the initial 12 weeks (Figures 1, 2, and 3).











Figure 3-Study 2012-0104:



Table 1 enumerates the number of patients in the safety samples for the induction phase in each of the three trials.

Study	Placebo	Brodalumab	Brodalumab	Ustekinumab
		140mg q2wks	210mg q2wks	
2012-0102	220	219	222	0
2012-0103	309	607	612	300
2012-0104	313	626	622	313
TOTAL	842	1452	1456	613

 Table 1: Enumeration of Patients in the Induction Phase of the Phase 3 Trials

Discontinuation rates during the induction phase for each treatment group for all three studies were low (less than 6% in Study 2012-0102 and less than 5% in the other two trials).

B. Psychiatric Inclusion/Exclusion Criteria

Subjects with moderate to severe psoriasis who had known comorbid psychiatric conditions such as depression, substance abuse, or prior suicidal behavior, were NOT initially excluded from the Phase 3 brodalumab trials. Basically, there were no psychiatric exclusion criteria in the Phase 3 initial study protocols. Some assessment of past psychiatric history (reported by subject or presence of psychiatric medication) was done at baseline screening visit as part of routine medical history, and if present was recorded in subjects' baseline medical history.

After concerns were raised in a February 2014 sponsor letter about a possible SIB signal, and after subsequent FDA discussion and recommendations, the electronic C-SSRS and PHQ-8 were added via protocol amendment in May 2014 to monitor subjects for suicidality and depression respectively. (See specific criteria below.) Subjects in the studies who were subsequently flagged by the revised screening scales were discontinued and referred to mental health professionals.

C. Psychiatric Safety Monitoring

The eC-SSRS and PHQ-8 were used to monitor psychiatric safety in their subjects starting in May 2014 (midway through these trials). These ratings were not performed during the induction phases of the three Phase 3 trials.

The eC-SSRS is a standardized and validated instrument developed for the assessment of the severity and frequency of suicidal ideation and behavior (Mundt et al, 2010; Posner et al, 2011). Subjects respond to standardized clinical questions that are presented in a uniform fashion. The eC-SSRS defines five subtypes of suicidal ideation and of behavior in addition to self-injurious behavior with no suicidal intent. The eC-SSRS takes approximately 3 to 10 minutes to complete.

The PHQ-8 is a validated and widely used eight-item version of the Patient Health Questionnaire depression scale designed to clinically assess patients for symptoms and signs of depression (Kroenke and Spitzer, 2002; Kroenke et al, 2009). The PHQ-8 takes approximately 3 minutes to complete.

The Hospital Anxiety and Depression Scale (HADS) a 14-item scale, to which the patient responds with a self-rating of 0-3 on 7 symptoms of depression and 7 symptoms of anxiety, was included to monitor subjects' psychiatric symptoms during one study's induction phase: it was collected at baseline and Week 12 in Study 2012-0102 only and in a small number of subjects.

After implementation of the eC-SSRS and PHQ-8, all subjects were reconsented to inform them of the potential risk of SIB and required to take these self-rated scales. Neither was implemented during the 12-week induction phase for any Phase 3 trials since that phase ended for all subjects by late 2013. The adverse events during that period were retroactively identified and adjudicated for classification via the Columbia Classification Algorithm of Suicide Assessment (C-CASA), as discussed in Sections D and E.

Any positive score on the C-SSRS (any report of SIB) triggered discontinuation from the study and a mental health referral. Any PHQ-8 score 10 or greater triggered mental health referral and 15 or greater triggered study discontinuation.

Primary analysis was to occur at week 12 and at withdrawal endpoints up until week 52 (which went on up until August 2014 for some subjects). Interim analyses were planned (to include the C-SSRS and PHQ-8) after 80% of subjects reached week 132 in the study, and after all subjects completed week 266, as well as annual safety analyses until the study was closed.

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The sponsor's coding of investigator adverse event terms to MedDRA preferred terms was evaluated by examination of adverse event datasets for the three Phase 3 trials. All events classified under the Psychiatric SOC were examined. In addition, it was discovered that the term "overdose" was classified under the Injury/Poisoning SOC. Overall, the coding of reported terms to preferred terms was acceptable.

E. Review of Psychiatric Adverse Event Data

SIB Event Identification

I reviewed the ADAE.xpt SIB dataset provided by the sponsor which includes all adverse events in the brodalumab Phase 3 trials up until a March 2015 data cutoff.

I screened for the MedDRA terms "suicide," "suicidal," "self-injury," and "overdose" for all phases of the Phase 3 studies. This review detected SIB events in the datasets such as: suicide attempts/behavior, suicidal ideation/thoughts, suicidal plan, self-injury, and completed suicide (some as overdose). My ADAE review revealed 36 events in 30 different subjects.

The sponsor also provided an ADSIB.xpt dataset intended to include all events they classified as SIB events based on the eC-SSRS and C-CASA adjudicated adverse event classifications. The ADSIB dataset included 33 events in 28 different subjects. The difference from my findings is explained by 2 subjects with events classified by the sponsor as non-treatment-emergent events and thus excluded from their ADSIB dataset. In both cases, it is not clear to me that the exclusion of these patients was justified. Thus, I have included them in rate calculations below.

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During the initial 12-week induction period only, my review noted 2 subjects with SIB events: 1 subject on brodalumab and 1 subject on ustekinumab. No one on placebo had any SIB events during that 12-week period. Incidence rates are not adjusted for exposure because dropout rates for both treatment groups during the induction phases were very low.

	Subjects	Events
Brodalumab	1	2
Ustekinumab	1*	2*
Placebo	0	0

Table 2: 12-Week Induction Phase Suicidal Events/S	Subjects
--	----------

*excluded by sponsor as non-treatment related, but included here

	Event Subjects/Total Subjects	Percentage
Brodalumab	1/2908	0.03%
Ustekinumab	1/613	0.16%
Placebo	0/842	0.00%

Table 3: Incidence based on the 12-week Induction Phase

Using a 2-tailed Fisher's exact test, the differences between the SIB rates for brodalumab versus placebo and brodalumab versus ustekinumab were not statistically significant at an alpha level of 0.05 (p-values of 0.22 and 0.32, respectively).

Incidence of Post-Induction Phase SIB Events

For the rest of the 52-week study period and extension phases, it is difficult to infer drug causality to SIB events because of the re-randomization that occurred at the start of this phase, which resulted in loss of the original randomized properties of the treatment groups. Therefore, I did not compute incidence or perform a comparative analysis of SIB rates.

There were 9 events that occurred during the rest of the 52-week period (1 was by the same individual who had 2 events in the induction phase 20120103-10366804033). Three of these events were on ustekinumab and 6 were on brodalumab.

	Subjects	Events		
Brodalumab	6 *	6 *		
Ustekinumab	3	3		
Placebo	n/a	n/a		

Table 4: Week 13 to Week 52 Suicidal Events/Subjects

*1 subject same as subject in Induction Phase

There were 21 more events by 18 subjects that occurred during an open-label follow-up extension phase during which all subjects received brodalumab (there was no placebo or active control arm). This phase was intended to continue for 5 years total but ended May 22, 2015. (There was 1 additional event by 20120103-10366001002 that the sponsor considered non-treatment-related. I will include this subject here.) This includes the data through March 2015.

Table 5: Follow-Up Extension Phase (2013-2014 through March 2015)

	Subjects	Events	-
Brodalumab	18*	21*	
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*1 subject excluded by sponsor but included here

There were 4 completed suicides overall, 2 occurring during the 52-week study (not during the induction period) and 2 during the open-label extension phase. All had been treated with brodalumab. (There have reportedly been 2 other suicides in the other brodalumab trials for psoriatic/rheumatoid arthritis.)

In addition, there was a 4-Month Safety Update Report sent by the sponsor in March 2016 which covered new adverse events for several months after the last ADAE dataset cut off in late March 2015. The safety data cutoff for this update was November 2015. Upon review, this set included 7 new SIB events all occurring April to July 2015 among subjects in post-induction phase of the Phase 3 trials (There was also 1 new SIB event from someone in another open-label study). 4 had suicidal ideation and 4 had suicide attempts; none were completed suicides, all had been actively exposed to brodalumab during the extension phase. (One had not taken brodalumab since 3 months prior though.)

F. Scale Data/Suicidality Assessment Report

The C-SSRS and PHQ-8 were routinely implemented midway through the Brodalumab study program as per FDA recommendation in late May 2014. To identify SIB events that occurred prior to this, the sponsor retroactively conducted a search of relevant MedDRA terms which were adjudicated for classification according to the C-CASA with a cutoff date of November 2014.

The implementation of these monitoring tools seem to have identified more SIB events during the later part of the trials and during the long-term extension period than were detected earlier in the trials. Per the sponsor, the reported rate of suicidal behavior almost doubled and the reported rate of suicidal ideation increased 10-fold after subjects began completing the eC-SSRS. The rate of completed suicides decreased slightly after implementation of the eC-SSRS.

Table 6: Suicidal adverse events in brodalumab psoriasis trials before and after eC-SSRS implementation (from sponsor)

		U			
		Pre	Post		
		eC-SSRS	eC-SSRS		
Event		N=4464	N=3823		
		Pyrs 5383.3	Pyrs 2530.2		
	n	Rate/100 pyrs	n	Rate/100 pyrs	
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Suicidal ideation	3	0.06	15	0.59	

So the exposure-adjusted rates of suicidal ideation and attempts were greater after implementation compared to the pre-C-SSRS period. However, these were not concurrent, randomized groups. There was confounding by time, so an alternative explanation to enhanced ascertainment is that the risk of events is higher with a longer duration of exposure. Also, there may be other uncontrolled factors at play due to lack of randomization.

The PHQ-8 detected more frequent mild score elevation in brodalumab versus ustekinumab, although one cannot extrapolate conclusions due to scale usage after the placebo-controlled induction phase.

For the HADS used in Study 2012-0102 only during the induction phase, the results showed improved scores in brodalumab versus placebo, but only a small number of the study subjects completed the scale; given the small number of subjects, the results are not reliable.

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and the relative infrequency of SIB events, although they felt that in comparison to "external controls" there seemed to be a higher than usual rate of completed suicides by people on brodalumab. They noted an uptick in SIB events after the implementation of the eC-SSRS and PHQ-8 in March 2014 and felt the incidence of SIB events was likely underestimated prior to the scales' usage. They could not determine based on the data afterwards though whether eC-SSRS reduced later rates of SIB behavior in the extension phases.

They felt that existing pharmacovigilance/epidemiology methods will not be adequate to assess the risk of SIB events with brodalumab during the post-marketing period, and given this concern and the limited data analyzability and concerning findings, they thought a Complete Response might have to be considered for brodalumab. Another recommendation if brodalumab was still approved would be to restrict the use of brodalumab to patients without a relevant past psychiatric history and/or to continue ongoing C-SSRS or comparable monitoring during usage, and to consider a REMS and appropriate labeling to help prescribers and patients to implement these recommendations.

However, it remains unclear in my opinion if such precautions would help prevent SIB events given that the data currently available for review is inconclusive.

IV. Conclusions and Recommendations

Based on the review of the pooled data from the 12-week placebo-controlled induction phase of the three Phase 3 psoriasis trials for brodalumab, no statistically significant association of SIB elevation was found for brodalumab versus placebo. However, the generalizability of this finding is limited by the relatively short duration of the study period, the overall rare incidence of SIB events, and the use of different scales and adjudication methods during different phases of the clinical trials to detect and classify SIB events (although the same method was used at least during the 12-week induction phase alone.) Also, the C-CASA method used during the induction phase is intuitively considered less sensitive at detecting SIB events than the eC-SSRS.

One might also consider a possible beneficial effect on depression and anxiety based on the HADS finding in one placebo-controlled study 2012-0102, where the brodalumab arm showed significant improvement in levels of depression/anxiety symptoms detected by the HADS versus placebo. Again though, the findings are limited by relatively small sample size and possible confounding (situational reaction to improved skin symptoms, etc.)

I have ongoing concerns about the lack of ability to make any definitive conclusions about the relationship between brodalumab and suicidality based on the existing data, and the adequacy of currently available pharmacovigilance methods to detect events during the postmarketing period, and whether any proposed REMS recommendations would be helpful in preventing suicides if the risk factors for SIB remain uncertain.

Given all this uncertainty, I recommend that the sponsor conduct an active-controlled, parallel group study with brodalumab focusing on frequent monitoring for psychiatric symptoms, especially suicidal ideation and behavior but also depressive symptoms. The active control agent should be a psoriasis agent which appears to have low risk for SIB events. This may permit

better understanding of the relationship between brodalumab treatment and SIB as well as determination of risk factors for SIB, which might inform a future REMS. It is further recommended that this study be conducted prior to approval, because of the current availability of safe and effective agents to treat psoriasis and the potential for fatal and other serious sequelae of suicidal behavior that might be produced by brodalumab treatment if a true causal relationship exists. This will likely have to be a large study of considerable length. DPP is willing to work with FDA dermatology experts, epidemiologists, and statisticians in designing such a trial.

As per general DPP recommendations, SIB events during clinical trials are best assessed prospectively using a validated instrument like the C-SSRS. The ongoing usage of such scales is highly recommended to detect systematically ongoing SIB events during future studies.

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JEAN S KIM 04/20/2016

/s/

PAUL J ANDREASON 04/20/2016

MITCHELL V Mathis 04/25/2016

CONSULTATIVE REVIEW AND EVALUATION OF CLINICAL DATA CONSULT #11562

Consultant Reviewer: Consultation Requestor: Subject of Request: Date of Request: Date Received: Desired Completion Date: Jean Kim MD, MA, Medical Officer, OND-ODE1-DPP Strother D. Dixon, RPM, ODE III, DDDP BLA 761032 (Brodalumab) 12/2/2015 12/3/2015 6/13/2016

I. Background

Brodalumab (also known as AMG 827) is a monoclonal antibody that selectively targets the human interleukin-17 receptor (IL-17R) and antagonizes the IL-17 pathway. It binds with high affinity to human IL-17R and blocks the biological activity of IL-17A, IL-17C, IL-17F, IL-17A/F heterodimer, and IL-25. It is has been developed to treat moderate to severe plaque psoriasis. The proposed dosing regimen is 210 mg subcutaneously at weeks 0, 1, and 2, followed by 210 mg every 2 weeks (Q2W). On August 12, 2015, Amgen, an original co-sponsor of brodalumab, withdrew their sponsorship and transferred it to the sole sponsorship of AstraZeneca.

DDDP had requested consultation with DPP in March 2014 to seek advice regarding psychiatric adverse events in Phase 3 trials after several reports of suicidal ideation or behavior (SIB) were reported to the Agency. The consultative review was completed by Cara Alfaro, Pharm.D., in July 2014 and recommended safety changes such as administration of the Columbia Suicide Severity Rating Scale (C-SSRS), cutoff scores for the Patient Health Questionnaire-8 (PHQ-8) or Beck Depression Inventory (BDI) for both study entry and for safety monitoring during the study, additional exclusion criteria to screen out severe SIB cases, and a quantitative analysis of the comparative SIB signal between treatment and control groups. The sponsor agreed to add the C-SSRS to monitor for SIB (which changed some of the exclusion criteria mid-study, in May 2014); the recommendations were communicated to them in meetings before DPP's review was finalized. There was also a blinded, independent adjudication of all potential SIB events identified from a list of MedDRA terms, with subsequent classification using the Columbia-Classification Algorithm for Suicide Assessment (C-CASA).

The Division of Psychiatry Products (DPP) has been consulted again by DDDP to review the data from the BLA submitted by AstraZeneca on November 17, 2015, and to provide input on safety concerns about psychiatric adverse effects associated with brodalumab, such as suicidal ideation and behavior, and to clarify whether these events are a primary drug effect or reflect the background occurrence of these events in a patient population that has higher rates of depression and suicidal ideation and behavior.

II. Review of Clinical Data

A. Selection of Relevant Clinical Trials

The efficacy of brodalumab is supported primarily by 3 global pivotal, Phase 3 placebo-controlled studies (2012-0102, 2012-0103, and 2012-0104).

For the purposes of this review, I will examine these 3 trials because they are similar in design and enrolled a larger number of patients compared to other studies in this program. These trials all began with a 12-week placebo-controlled induction phase that will be the focus of this review. Subsequent to that phase of each study, patients were re-randomized to drug, placebo, or active control, rendering cross-treatment comparisons unreliable primarily because of loss of the randomized character of the treatment groups beyond the initial 12 weeks (Figures 1, 2, and 3).











Figure 3-Study 2012-0104:



Table 1 enumerates the number of patients in the safety samples for the induction phase in each of the three trials.

Study	Placebo	Brodalumab	Brodalumab	Ustekinumab
		140mg q2wks	210mg q2wks	
2012-0102	220	219	222	0
2012-0103	309	607	612	300
2012-0104	313	626	622	313
TOTAL	842	1452	1456	613

 Table 1: Enumeration of Patients in the Induction Phase of the Phase 3 Trials

Discontinuation rates during the induction phase for each treatment group for all three studies were low (less than 6% in Study 2012-0102 and less than 5% in the other two trials).

B. Psychiatric Inclusion/Exclusion Criteria

Subjects with moderate to severe psoriasis who had known comorbid psychiatric conditions such as depression, substance abuse, or prior suicidal behavior, were NOT initially excluded from the Phase 3 brodalumab trials. Basically, there were no psychiatric exclusion criteria in the Phase 3 initial study protocols. Some assessment of past psychiatric history (reported by subject or presence of psychiatric medication) was done at baseline screening visit as part of routine medical history, and if present was recorded in subjects' baseline medical history.

After concerns were raised in a February 2014 sponsor letter about a possible SIB signal, and after subsequent FDA discussion and recommendations, the electronic C-SSRS and PHQ-8 were added via protocol amendment in May 2014 to monitor subjects for suicidality and depression respectively. (See specific criteria below.) Subjects in the studies who were subsequently flagged by the revised screening scales were discontinued and referred to mental health professionals.

C. Psychiatric Safety Monitoring

The eC-SSRS and PHQ-8 were used to monitor psychiatric safety in their subjects starting in May 2014 (midway through these trials). These ratings were not performed during the induction phases of the three Phase 3 trials.

The eC-SSRS is a standardized and validated instrument developed for the assessment of the severity and frequency of suicidal ideation and behavior (Mundt et al, 2010; Posner et al, 2011). Subjects respond to standardized clinical questions that are presented in a uniform fashion. The eC-SSRS defines five subtypes of suicidal ideation and of behavior in addition to self-injurious behavior with no suicidal intent. The eC-SSRS takes approximately 3 to 10 minutes to complete.

The PHQ-8 is a validated and widely used eight-item version of the Patient Health Questionnaire depression scale designed to clinically assess patients for symptoms and signs of depression (Kroenke and Spitzer, 2002; Kroenke et al, 2009). The PHQ-8 takes approximately 3 minutes to complete.

The Hospital Anxiety and Depression Scale (HADS) a 14-item scale, to which the patient responds with a self-rating of 0-3 on 7 symptoms of depression and 7 symptoms of anxiety, was included to monitor subjects' psychiatric symptoms during one study's induction phase: it was collected at baseline and Week 12 in Study 2012-0102 only and in a small number of subjects.

After implementation of the eC-SSRS and PHQ-8, all subjects were reconsented to inform them of the potential risk of SIB and required to take these self-rated scales. Neither was implemented during the 12-week induction phase for any Phase 3 trials since that phase ended for all subjects by late 2013. The adverse events during that period were retroactively identified and adjudicated for classification via the Columbia Classification Algorithm of Suicide Assessment (C-CASA), as discussed in Sections D and E.

Any positive score on the C-SSRS (any report of SIB) triggered discontinuation from the study and a mental health referral. Any PHQ-8 score 10 or greater triggered mental health referral and 15 or greater triggered study discontinuation.

Primary analysis was to occur at week 12 and at withdrawal endpoints up until week 52 (which went on up until August 2014 for some subjects). Interim analyses were planned (to include the C-SSRS and PHQ-8) after 80% of subjects reached week 132 in the study, and after all subjects completed week 266, as well as annual safety analyses until the study was closed.

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Table 5: Follow-Up Extension Phase (2013-2014 through March 2015)

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		Pre	Post		
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JEAN S KIM 04/20/2016

/s/

PAUL J ANDREASON 04/20/2016

MITCHELL V Mathis 04/25/2016

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service Food and Drug Administration Center for Devices and Radiological Health Office of Compliance, Division of Manufacturing & Quality Respiratory, ENT, General Hospital, Ophthalmic Device Branch (REGO)

Date:	March 30, 2016	
То:	Gary Chiang, MD, CDER/OND/ODEIII/DDDP Gary.Chiang@fda.hhs.gov	
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	RPM: Strother D. Dixon	
Through:	Viky Verna, Chief, REGO, DMQ, OC, CDRH Digitally signed by Viky Verna -5 DN: C:US, Government, Our=HHS, Our=FDA, Our=Pople, C-Wiky Verna -5, 0:92342.19200300.101.1=2000495623 Date: 2016.04.07 15:28.41-0400	
From:	Crystal Lewis, REGO, DMQ, OC, CDRH	
Applicant:	AstraZeneca 2 Kingdom St London, UK W26BD FEI# 3012051785	
Application #	BLA761032	
Consult #	ICC#1500652	
Product Name:	Brodalumab	
Pre-Approval Inspection	on: No	
Documentation Review	w: No Additional Information Required	
Final Recommendatio	n: APPROVAL	

The Office of Compliance at CDRH received a consult request from CDER to evaluate the applicant's compliance with applicable Quality System Requirements for the approvability of BLA761032.

PRODUCT DESCRIPTION

Brodalumab is a IL-17a receptor inhibitor that is intended for the treatment of moderate to severe plaque psoriasis. The final combination product is provided as a sterile, single use,

preservative free solution for subcutaneous injection in a prefilled syringe (PFS) (^{b) (4)}. The sterile prefilled syringe contains 140mg/ml brodalumab in 30 mM glutamate, 2.4% (w/v) proline, and 0.01% (w/v) polysorbate 20, pH 4.8, filled to deliver a 1.5mL in a 1ml volume which provides 210mg of Brodalumab.

REGULATORY HISTORY

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



Responsibility – The firm is responsible for the final assembly and packaging for the final combination product.

Inspectional History – An analysis of the firm's inspection history over the past 2 years showed that an inspection conducted on ^{(b) (4)}. The inspection covered drug GMP policies and was classified VAI.

Inspection Recommendation:

(1) An inspection is <u>not</u> required because:

• The firm has received a drug inspection which covered GMP requirements within the last two years. The inspection was acceptable therefore a preapproval inspection is not required.

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

DOCUMENTATION REVIEW

Management Control, 21 CFR 820.20

^{(b) (4)} management responsibilities are outlined and defined in their Quality Policy documents. An organizational structure with roles, responsibilities and authorities are defined communicated and implemented in every part of the organization. ^{(b) (4)} states management is responsible for implementing an effective Quality Management System (QMS) and reviewing this system regularly to ensure the firm's quality objectives are met. QMS requirements, procedures, and records are retained in a document management system that has been validated. The firm also performs audits of the QMS to assess compliance and effectiveness.

The information provided by the firm has <u>adequately</u> addressed the requirements of 21 CFR 820.20.

Design Control, General, 21 CFR 820.30

Design and development, Design Input, Design Review, Design Verification and Validation, and Design Transfer planning processes are defined in the firm's device design controls. Prior to implementation, the firm reviews Design Changes for potential impact to safety and quality and these changes are then verified and/or validated prior to implementation. The Device Master Records and Design History File (DHF) documents are retained in a document management ^{(b) (4)} maintains accountability for the combination product system that has been validated. design controls including combination product design verification, design validation, and drugdevice interaction testing. The firm also maintains the combination product DHF for the PFS (b) (4) (b) (4) ^{(b) (4)} who is responsible for the . The device DHF is retained by details the design control responsibilities in the Design and Development Plans ^{(b) (4)} and ^{(b) (4)}. The location and maintenance and in the agreements between $^{(b)}$ (4) can be found in the responsibilities for all design control documentation for the PFS (b) (4) Design History File Index.

The information provided by the firm has <u>adequately</u> addressed the requirements of 21 CFR820.20.

Purchasing Controls, 21 CFR 820.50

Multiple suppliers are contained within ^{(b) (4)} Purchasing Controls and the material related programs and processes developed by the firm. These processes were developed to assure materials and components consistently meet GMP requirements. ^{(b) (4)} qualifies its GMP suppliers, contractors and consultants to provide goods and services. Quality agreements are instituted with component/sub assembly suppliers and design partners for the Brodalumab combination product and its device constituent parts. Also, included within these agreements are sub-contractors.

The information provided by the firm has <u>adequately</u> addressed the requirements of 21 CFR 820.50.

Corrective and Preventive Action (CAPA), 21 CFR 820.100

^{(b) (4)} corrective and preventive action (CAPA) system contains the process for initiating corrective and preventive actions. The decision to initiate action is according to inputs such as nonconformances, complaints, returned product, risk assessments, audits, inspections and trends. Once issues are identified, they are investigated to determine a root cause. This includes reviewing CAPA records and assessing the potential impact to product quality. Changes occurring as a result of the CAPA program are managed through the change control process. The CAPA is then evaluated to confirm the actions taken have been effective.

The information provided by the firm has <u>adequately</u> addressed the requirements of 21 CFR820.100.

Installation, 21 CFR 820.170

Installation is not required for this combination product.

Servicing, 21 CFR 820.200

Servicing is not required for this combination product.

MANUFACTURING

Production and Process Controls

^{(b) (4)} detailed the history of the drug product process in its Process Development History (140mg/ml PFS). The firm also described the summary of the process design which includes a commercial control strategy. This strategy includes characterization studies and at-site commercial scale runs. The firm implored small scale studies to define the process and engineering runs to demonstrate the process met commercial scale requirements for product quality.

^{(b) (4)} also describes its process evaluation and establishment of process performance qualification strategy. The firm established validation criteria based on knowledge from process development and process characterization studies, commercial-scale experience and monoclonal antibody processes.

(b) (4)

Production Flow

Acceptance Activities The firm's documentation for Acceptance Activities were not found.

RECOMMENDATION

CDRH/OC recommends APPROVAL for Brodalumab – #BLA761032.

 Crystal
 Digitally signed by Crystal Lewis -S DN: c=US, o=US. Government, ou=HHS, ou=EDA, ou=People, c=Crystal Lewis -S 0.92342, 19200300.100.1.=20004301

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 Date: 2016.04.07 15:42:13 -0400'

Crystal Lewis

Prepared: CLewis: 03/30/16 Reviewed: VVerna: 04/07/16

CTS No.: ICC1500652 BLA761032

Review Cycle Meeting Attendance: Month/Day/Year Month/Day/Year Month/Day/Year

Inspectional Guidance

Firm to be inspected:

(b) (4)

CDRH recommends the inspection under the applicable Medical Device Regulations of ^{(b) (4)}

A comprehensive baseline Level 2 inspection is recommended focusing on Management Responsibility (21 CFR 820.20), Purchasing Controls (21 CFR 820.50), CAPA (21 CFR 820.100), Final Acceptance Activities (21 CFR 820.80), and Design Controls (21 CFR 820.30)

Additionally, evaluate the manufacturing activities associated with the manufacturing/assembly of the finished combination product, including in process and final acceptance activities. Detailed inspection guidance will be provided upon request.

REGULATORY STRATEGY

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

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

Primary Contact

Crystal Lewis CSO, REGO DMQ Office of Compliance, WO66 RM 3452 Phone: 301-796-6116

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

Viky Verna Chief REGO DMQ Office of Compliance, WO66 RM 3435 Phone: 301-796- 2909

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

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

/s/

STROTHER D DIXON 04/14/2016

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

Epidemiology: Review of Clinical Trial Data

Date:	March 22, 2016
Reviewer(s):	Andrew D. Mosholder, MD, MPH, Medical Officer Division of Epidemiology I
	Gabriella Anic, PhD, MPH, Epidemiologist Division of Epidemiology I
Team Leader	Sukhminder K. Sandhu, PhD, MPH, MS, Team Lead Division of Epidemiology I
Division Director	Simone P Pinheiro, Associate Director Division of Epidemiology 1
Subject	Risk of suicide in patients treated with brodalumab
Drug Name(s):	Brodalumab
Application Type/Number:	BLA 761032
Applicant/sponsor:	AstraZeneca
OSE RCM #:	2015-686

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EXECUTIVE SUMMARY

The purpose of this review is for the Division of Epidemiology I (DEPI-I) to evaluate data on suicidal ideation and behavior (SIB) events in brodalumab clinical trials, and to summarize available information on suicide rates in psoriasis patients treated with biologics in clinical trials to assist the Division of Dermatology and Dental Products (DDDP) in determining regulatory action on the pending brodalumab biologics license application (BLA). Brodalumab is a monoclonal antibody against the interleukin 17 (IL-17) receptor A. The brodalumab BLA is under review for the indication of moderate to severe plaque psoriasis in adults who are candidates for systemic therapy or phototherapy.

In early 2014, safety monitoring identified suicidal ideation and behavior (SIB) as a safety concern in the brodalumab clinical trials. The sponsor (Amgen at the time) sent a letter to investigators of all trials, although it did not specify whether these SIB events were only observed in the psoriasis trials. The letter stated that Amgen was revising the informed consent document to reflect the occurrence of SIB; investigators were asked to re-consent all subjects when the new document became available. Soon after, Amgen implemented risk-mitigation strategies, including use of two self-rated scales, the electronic Columbia-Suicide Severity Rating Scale (eC-SSRS) and the Patient Health Questionnaire-8 (PHQ-8), to monitor subjects for depression and suicidality in ongoing brodalumab trials for all indications. A total of 6 brodalumab-treated subjects in clinical trials committed suicide, or roughly 1 per 1,000 treated; 4 suicides occurred prior to implantation of the risk mitigation strategies, and 2 occurred after they were in place. Concern about SIB led Amgen to discontinue all ongoing clinical trials.

This review finds:

- 1. Meaningful comparisons of brodalumab SIB rates to placebo or active controls are not available from the brodalumab development program, because of the short duration of exposure to those comparators, and the relative infrequency of SIB event.
- 2. Comparisons to external controls indicate an inordinate number of completed suicides in brodalumab clinical trials.
- 3. The incidence of suicidal behavior and ideation was likely to have been underestimated prior to use of the eC-SSRS.
- 4. Though the eC-SSRS improved ascertainment of SIB, the data are not adequate to determine whether the eC-SSRS reduced the rate of attempted or completed suicide.
- 5. There does not appear to be a good rationale for separating data on SIB in psoriasis trials from SIB data in other indications.
- 6. Data on psychiatric adverse events other than SIB do not suggest a relationship to brodalumab, but the ability to detect adverse mental effects in the trials was probably limited.

2

7. Existing pharmacovigilance and pharmacoepidemiology methods will not be adequate to assess the risk of SIB with brodalumab in the post-marketing environment.

Although a causal relationship of SIB to brodalumab use is uncertain, to the extent there is currently "insufficient information about the drug to determine whether the product is safe for use," DDDP may need to consider a Complete Response per 21 CRF 313.125(b)(4).

If brodalumab is approved, restricting its use to patients without a relevant past psychiatric history would reduce the number of SIB events among brodalumab users, regardless of the extent to which SIB events are causally related. Clinical monitoring of users with the eC-SSRS would greatly improve the chances of detecting SIB, so that patients could be directed to obtain treatment and discontinue brodalumab. A REMS could be considered to help implement these practices. Appropriate labeling and a Medication Guide would help communicate this issue to prescribers and patients. Finally, no postmarketing observational data collection would be recommended, given the limitations of such data for suicidal outcomes.

1 INTRODUCTION

1.1 BACKGROUND

The purpose of this review is to evaluate data on suicides and suicidal ideation and behavior (SIB) in clinical trial data for brodalumab, and to provide available data on the rates of suicidal behavior in psoriasis patients in clinical trials. The Division of Dermatology and Dental Products (DDDP) consulted DEPI-I as part of their review of BLA 761032 for brodalumab in the treatment of moderate to severe plaque psoriasis in adults. Brodalumab is a human monoclonal antibody that binds to the interleukin-17 (IL-17) receptor A, thus blocking the pro-inflammatory effects of the interleukins IL-17A, IL-17C, IL-17F, IL-17A/F heterodimer, and IL-25. This is thought to be brodalumab' s mechanism of action in psoriasis, but a biologic mechanism by which brodalumab might cause mental effects or increase the risk of suicide is not known.

Multiple observational studies have reported that psoriasis patients have a higher rate of psychiatric disorders including anxiety, depression, and suicidality (1-7). A populationbased cohort study that used data from patient's electronic medical records in the General Practice Research Database (now named the Clinical Practice Research Datalink), found the risk of suicidality (defined as diagnosis of suicidal ideation, suicide attempt, or suicide) was significantly higher in psoriasis patients compared to patients without psoriasis (hazard ratio = 1.44, 95% confidence interval = 1.32-1.57) (6). The same study estimated that psoriasis patients had an overall suicidality rate of 0.09 per 100 person-years; the publication did not provide specific rates for suicide, suicidal ideation or suicide attempt. An analysis using data form the National Health and Nutrition Examination Survey, a study representative of the general US population, also found that a history of psoriasis was significantly associated with a higher risk of major depression (odds ratio = 2.09, 95% confidence interval = 1.41-3.11) (7). In early 2014, safety monitoring identified suicidal ideation and behavior (SIB) as a safety concern in the brodalumab clinical trials. The sponsor (Amgen at the time) sent a letter to investigators of all trials, although it did not specify whether these SIB events were only observed in the psoriasis trials. The letter stated that Amgen was revising the informed consent document to reflect the occurrence of SIB; investigators were asked to re-consent all subjects when the new document became available. Soon after, the sponsor implemented risk-mitigation strategies, including use of two self-rated scales, the electronic Columbia-Suicide Severity Rating Scale (eC-SSRS) and the Patient Health Questionnaire-8 (PHQ-8), to monitor subjects for depression and suicidality in ongoing brodalumab trials for all indications. A positive eC-SSRS, which is reporting any suicidal ideation or behavior, triggered a mental health referral and discontinuation of treatment. Similarly, a PHQ-8 score ≥ 10 triggered mental health referral, and subjects with a PHQ-8 score ≥ 15 discontinued treatment. Clinical trials proceeded with this monitoring for over a year, then Amgen elected to discontinue all brodalumab trials (see below).

1.2 REGULATORY HISTORY

The following is the relevant regulatory history timeline with regard to the suicide safety concern for brodalumab:

- August 27, 2009: Amgen submits an Investigational New Drug (IND) Application for brodalumab (formerly known as AMG 827).
- February 6, 2014: Amgen issues a Dear Investigator letter describing SIB events in brodalumab clinical trials. The letter did not specify whether the SIB events occurred in the psoriasis trials or in trials for another indication. Shortly thereafter, Amgen implements the risk mitigation measures noted above, and begins submitting monthly updates on suicidal events in ongoing trials.
- March 16, 2015: FDA requests a meeting with Amgen to discuss the potential risk of SIB in the brodalumab development program.
- May 13, 2015: FDA meets with Amgen for brodalumab to discuss the suicidality signal observed in the clinical trial data. In response to this meeting, Amgen decides not to submit the BLA for brodalumab.
- May 29, 2015: Amgen communicates to FDA their decision to discontinue all subjects from ongoing brodalumab clinical trials.
- August 12, 2015: Amgen transfers the brodalumab IND to co-developer AstraZeneca.
- October 21, 2015: FDA and AstraZeneca hold a pre-BLA meeting.
- November 16, 2015: AstraZeneca submits BLA 761032 for brodalumab in the treatment of moderate to severe plaque psoriasis, in adults who are candidates for systemic therapy or phototherapy.

2 MATERIALS REVIEWED

- "Brodalumab 13 May 2015 FDA Meeting, Potential Risk of Suicide Ideation and Behavior," submitted by Amgen on April 13, 2015.
- "Adverse Event Rates in Psoriasis or Psoriatic Arthritis, Final Technical Report," March 19, 2015. Prepared by Exponent for Amgen and submitted by Amgen on April 13, 2015.
- Brodalumab BLA Clinical Overview, dated October 21, 2015
- Brodalumab BLA Summary of Clinical Safety, Appendix 1: Potential risk of suicidal ideation and behavior ("SIB Supplement"), dated October 22, 2015.
- Brodalumab Monthly Safety Report #18 Suicidal Behavior and Suicidal Ideation (Report Date: 10 November 2015)
- 6-Month Cumulative Report, Suicidal Ideation and Behavior and Related Events in the Brodalumab Program (Date: 08 December 2015)
- "Columbia Classification Algorithm of Suicide Assessment Brodalumab" (Amgen, undated)
- Clinical trial data from other regulatory submissions for biologics and nonbiologics for the treatment of moderate to severe psoriasis.

3 REVIEW RESULTS

3.1 INCIDENCE OF SUICIDE BEHAVIOR IN BRODALUMAB CLINICAL TRIALS

3.1.1 Overview of clinical development program

Most trials were for the indication of psoriasis, but other indications included psoriatic arthritis, rheumatoid arthritis, asthma, and Crohn's disease. Design characteristics of various Phase III trials included 12-week double blind comparisons to placebo and to ustekinumab, re-randomizations after 12 weeks, 52 weeks of treatment with ustekinumab as a comparator, and extended open label brodalumab treatment beyond 52 weeks. The sponsor pooled safety data for analysis according to these designs and treatment periods.

The following summarizes the overall exposure to brodalumab in clinical trials. Subjects were typically seen one final time for an end-of-treatment follow-up visit after their last dose; the total exposure time shown for psoriasis subjects includes an average of 6-7 weeks of follow-up time after the last dose of brodalumab.

Dataset	N	Exposure in patient-years
Brodalumab, all trials (source: monthly safety report #18)	6,240	10,438
Brodalumab, psoriasis trials only (cutoff March 2015)	4,464	7,895

Among psoriasis subjects, approximately 70% were male, 90% were white, and 57% were 40 to 64 years old.

3.1.2 Incidence of SIB events in brodalumab trials

3.1.2.1 Placebo-controlled trials

Table 8 from the sponsor's SIB Supplement in the BLA submission, reproduced below, shows the incidence of SIB in the 12-week <u>double-blind portion</u> of the brodalumab psoriasis trials. The data were sparse, with a total of one event, a suicide attempt by a brodalumab subject.

Table 8 Subject in Integrate	ncidence o d Safety A	of SIB events d Analysis Set – I	uring the initial double-blind period Psoriasis Subset		
				Brodalumab	
	Placebo (N = 879) u (%)	Ustekinumab (N = 613) n (%)	140 mg Q2W (N = 1491) n (%)	210 mg Q2W (N = 1496) n (%)	All (N = 3066) n (%)
Suicidal behavior adverse event	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.07)	1 (0.03)
Suicide attempt	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.07)	1 (0.03)
Completed suicide	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Suicidal ideation adverse event	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

Source: SIB supplement

3.1.2.2 Active comparator data

If one considers the first 52 weeks of exposure to brodalumab, that person-time can be compared to the 52 weeks of exposure to ustekinumab (i.e., the sponsor's "Pool B"). The following summarizes the incidence of suicide events in psoriasis subjects during that 52 week exposure (source: SIB supplement Table 10), with 95% confidence intervals calculated by DEPI. There were two completed suicides with brodalumab and none with ustekinumab, though the patient-years of exposure was much higher for brodalumab, so meaningful comparisons are difficult.

Treatment (through week 52)	Ustekinumab	Brodalumab
Ν	613	4019
Patient-years	503.6	3545.7
Suicidal ideation (n)	1	3
Suicide attempt (n)	1	2
Completed suicide (n)	0	2
Suicidal ideation (rate per 100 pyrs)	0.199 (0.005, 1.105)	0.085 (0.017, 0.247)
Suicide attempt (rate per 100 pyrs)	0.199 (0.005, 1.105)	0.056 (0.007, 2.037)
Completed suicide (rate per 100 pyrs)	0	0.056 (0.007, 2.037)

The sponsor also analyzed the most severe eC-SSRS scores recorded during the same 52 weeks of exposure in psoriasis trials; these data are shown below (source: SIB supplement Table 30). Data are only shown for subjects who had at least one on-treatment eC-SSRS (regardless of

Suicide risk for brodalumab DEPI-I review.doc 3-22-2016

score), so the sample size is smaller than above. As the eC-SSRS was implemented while the trials were in progress, rates per 100 person years could not be calculated. The events were numerically somewhat more frequent with brodalumab, but comparisons should be made cautiously as the ustekinumab group had only 3 events and much fewer patient-years of follow-up.

Treatment through Week 52	Ustekinumab	Brodalumab
Subjects with eC-SSRS scores (n)	114	795
Suicidal ideation or behavior positive on eC-SSRS, n(%)	3 (2.6)	32 (4.0)

3.1.2.3 All trials

The table below was included in Amgen's pre-BLA meeting package, and presents the incidence rate of suicide behavior in the 4,464 psoriasis patients who received ≥ 1 dose of brodalumab through March 2015. (Identical data are in Table 14 of the AstraZeneca BLA SIB Supplement.) There were a total of 11 events among psoriasis subjects classified as suicidal behavior, including seven suicide attempts and four completed suicides.

The range of time between first active dose of brodalumab and attempted and completed suicides was 40-754 days and 97-845 days, respectively. Three of the four completed suicides for brodalumab in psoriasis patients occurred outside of the exposure period (i.e., >14 days after last active dose); those suicides occurred 19, 27, and 58 days after last active treatment. Two of the four suicide attempts also occurred outside the exposure period at 16 and 17 days after last active dose of brodalumab.

Table 1. Incidence rates per 100 patient-years of suicide behavior by MedDRA Preferred Term from first dose of brodalumab through March 2015 (psoriasis trials) (Source: Amgen pre-BLA package).

	Brodalumab				
		Subjects with	Brodalumab	Exposure Only	
	210 mg Q2W	Overall			
	After	Variable	Overall	Overall	
	Ustekinumab	Dosing	140 mg Q2W	/ 210 mg Q2W	All
	(Subj-yr	(Subj-yr	(Subj-yr	(Subj-yr	(Subj-yr
Events of Interest Category	=602.5)	=4567.8)	=435.6)	=2288.6)	=7894.6)
Preferred Term	(N = 567)	(N = 2327)	(N = 269)	(N = 1301)	(N = 4464)
	n (r)	n (r)	n (r)	n (r)	n (r)
Suicidal Ideation and Behavior	2 (0.33)	10 (0.22)	0 (0.00)	14 (0.61)	26 (0.33)
Complete suicide	0 (0.00)	0 (0.00)	0 (0.00)	4 (0.17)	4 (0.05)
Completed suicide	0 (0.00)	0 (0.00)	0 (0.00)	3 (0.13)	3 (0.04)
Intentional overdose	0 (0.00)	0 (0.00)	0 (0.00)	1 (0.04)	1 (0.01)
Suicidal behavior adverse event	0 (0.00)	4 (0.09)	0 (0.00)	7 (0.31)	11 (0.14)
Completed suicide	0 (0.00)	0 (0.00)	0 (0.00)	3 (0.13)	3 (0.04)
Suicide attempt	0 (0.00)	2 (0.04)	0 (0.00)	2 (0.09)	4 (0.05)
Intentional overdose	0 (0.00)	0 (0.00)	0 (0.00)	1 (0.04)	1 (0.01)
Suicidal behavior	0 (0.00)	1 (0.02)	0 (0.00)	1 (0.04)	2 (0.03)
Intentional self-injury	0 (0.00)	1 (0.02)	0 (0.00)	0 (0.00)	1 (0.01)
Suicidal ideation adverse event	2 (0.33)	8 (0.18)	0 (0.00)	8 (0.35)	18 (0.23)
Suicidal ideation	2 (0.33)	7 (0.15)	0 (0.00)	8 (0.35)	17 (0.22)
Depression suicidal	0 (0.00)	1 (0.02)	0 (0.00)	0 (0.00)	1 (0.01)

MedDRA v. 17.1; N= subjects in Studies 20090062/20090403, 20120102, 20120103, and 20120104 with ≥ 1 dose of brodalumab

The above rates are for patients treated with brodalumab (including some who received brodalumab after starting with ustekinumab) in the psoriasis clinical trials, as of the cutoff date of Mach 2015. The columns present SIB rates for different doses of brodalumab and then among all 4,464 psoriasis patients treated with brodalumab. To derive rates for all brodalumab trials, we used the data in the Monthly Safety Reports; specifically, from Tables 1 and 2, Monthly Safety Report #18. The following shows the event counts for all brodalumab-treated subjects, regardless of indication.

> Brodalumab-treated subjects, all trials N=6,240 Person-years = 10,438 Completed suicide (n) = 6Suicide attempts/behavior (n) = 15Suicidal ideation (n) = 18

Accordingly, in all clinical trials, 1 in 1,040 brodalumab-treated subjects committed suicide. The rate of completed suicide among all brodalumab-treated subjects was 0.06 per 100 person-years, or, in the more customary format for suicide rates, 57.5 per 100,000 person-years.

3.1.2.4 Impact of past psychiatric history

AstraZeneca conducted a subgroup analysis to assess the effect of past psychiatric history on the rate of SIB events. Past psychiatric history was obtained from the baseline clinical visit or the eC-SSRS, administered later in the study. The eC-SSRS includes a question regarding lifetime history of suicidality; for earlier trial subjects who did not complete an eC-SSRS, past history of suicidality was determined from the baseline medical history. (The sponsor noted that for the purpose of determining a past history of suicidality, the eC-SSRS appeared to have greater sensitivity than the routine medical history.) Either a reported history of depression at baseline, or concomitant antidepressant use (apparently without regard to specific indication) defined the subgroup of patients with prior depression. The table below displays the rates of SIB events by past psychiatric history.

p50114515 545	Jeeus				
	Past Depression Pyr=931.1 N=602	No Depression Pyr=6197.7 N=3671	Past Suicidality Pyr=196.3 N = 119	No Suicidality Pyr=6454.2 N = 3518	Suicidality unknown* Pyr=478.3 N=636
Event	n (rate per 100	n (rate per	n (rate per 100	n (rate per 100	n (rate per 100
	pyrs)	100 pyrs)	pyrs)	pyrs)	pyrs)
Suicidal ideation					
and behavior	13 (1.40)	13 (0.21)	7 (3.57)	8 (0.12)	11 (2.30)
Completed suicide	1 (0.11)	3 (0.05)	0 (0.00)	1 (0.02)	3 (0.63)
Suicidal behavior	5 (0.54)	6 (0.10)	3 (1.53)	3 (0.05)	5 (1 .05)
Suicidal ideation	10 (1.07)	8 (0.13)	6 (3.06)	6 (0.09)	6 (1 .25)

Table 2	. Rates of SIB	events according to	prior psychiatric	history,	brodalumab
psoriasi	is subjects				

Source: SIB supplement Table 22 Pyr, person-year

*Subjects whose eC-SSRS responses could not distinguish lifetime history versus trial events

The figure below provides a DEPI summary of these data. A past history of depression or suicidality substantially increased the rate of reported SIB events among brodalumab-treated psoriasis patients.



Figure 1. Suicide ideation and behavior by past psychiatric history. Source: SIB supplement Table 22

3.1.2.5 Impact of implementing eC-SSRS monitoring

Implementation of the eC-SSRS occurred while the trials were in progress. To assess the impact that eC-SSRS monitoring had on the rates of SIB events, AstraZeneca subdivided the brodalumab person-time according to whether the eC-SSRS was in use. The table below displays the findings.

Table 3. Suicidal adverse events in brodalumab psoriasis trials before and after
implementation of eC-SSRS monitoring

	-			-		
		Pre	Post			
Event		eC-SSRS	eC-SSRS			
		N=4464	N=3823			
		Pyrs 5383.3	Pyrs 2530.2			
	n Rate/100 pyrs		n	Rate/100 pyrs		
Completed suicide	3	0.06	1	0.04		
Any suicidal behavior	6	0.11	5	0.20		
Suicidal ideation	3	0.06	15	0.59		

Source: SIB appendix Table 32. Pyrs = person-years

The reported rate of suicidal behavior almost doubled (from 0.11 to 0.20 per 100 personyears), and the reported rate of suicidal ideation increased10-fold (from 0.056 to 0.59 per 100 person-years), after subjects began completing the eC-SSRS. The rate of completed suicides decreased from 0.06 to 0.04 per 100 person years. The ratio of rates of suicidal behavior to completed suicide increased with use of the eC-SSRS from1.83 to 5.0; as suicide attempts are generally much more common than completed suicides, this change in the ratio would be consistent with improved ascertainment of suicide attempts.

3.1.2.6 C-CASA adjudication

Amgen performed a partial adjudication of possible SIB events using the Columbia Classification Algorithm of Suicide Assessment (C-CASA) and the results were submitted with AstraZeneca's BLA. This is a retrospective blinded adjudication method for suicidal events in clinical trial data, developed by Columbia University (8) and employed in FDA's meta-analysis of suicidal events in antidepressant clinical trials (9). This method retrospectively classifies possible suicidal events, identified in a search of the clinical trial adverse event database, into one of eight categories.¹ Importantly, the sponsor only adjudicated events predating use of the eC-SSRS, and used a cutoff date of November 18, 2014. This adjudication classified 16 subjects as having suicidal events out of 1217 subjects with possible events. They adjudicated 4 of the 6 total completed suicides, confirming 3 and classifying one (subject 10216004001) as having insufficient information. Of 6 events previously classified as suicide attempts, 4 were downgraded, but the adjudication identified 3 newly recognized suicide attempts.

The sponsor concluded that the C-CASA adjudication did not have a substantive effect on the total number of SIB events. As noted, the sponsor only adjudicated part of the brodalumab clinical trial data, so a fully C-CASA adjudicated dataset of suicidal events is not available.

3.1.2.7 Listing of all SIB cases in brodalumab trials

We prepared a table listing, Appendix A, all of the cases of suicide, suicide attempt, suicidal behavior, and suicidal ideation in the brodalumab clinical trials, using information in the BLA and the monthly safety reports. Clinical narratives were available for all SIB events except a suicide behavior that occurred in a patient treated with placebo for asthma (study ID 2014043293). Some observations from inspection of this list follow:

- Initial reports of many events of suicidal ideation, and of some suicidal behaviors, came via the eC-SSRS rather than routine clinical monitoring.
- Many SIB events occurred in the setting of one or more psychosocial stressors.
- At the time of the SIB events, there was a wide range for treatment duration, and some events occurred after treatment was discontinued. Among all brodalumab

¹ Completed suicide, suicide attempt, preparatory acts toward imminent suicidal behavior, suicidal ideation, self-injurious behavior/no suicidal intent, other/no deliberate harm, self-injurious behavior/suicidal intent unknown, not enough information.

SIB cases, the median time from the first dose was 525 days, and the median time since the last dose was 14 days.

- Some of the suicidal ideation events disclosed on the eC-SSRS, had they been adjudicated using the C-CASA system, might not have been confirmed (e.g., two suicidal ideation events were in fact merely dreams with suicidal content).
- Many subjects with SIB had past histories of psychiatric disorders (for details, please see the sponsor's analysis of this, below). However, among the 6 completed suicides, only 2 had a positive psychiatric history.
- Most subjects with SIB discontinued brodalumab following the event. Accordingly, there is limited information on whether SIB might resolve despite continued brodalumab exposure. One exception was subject 10366084033, who continued brodalumab treatment after his first suicide attempt, then attempted suicide twice more during brodalumab treatment.
- Several of the suicide attempts, though unsuccessful, showed serious intent (two subjects made attempts with car exhaust, one subject put a gun to his head, one subject was found on a railroad track).
- There was no discernible pattern of premonitory signs or symptoms by which to predict suicidal behavior (e.g., two subjects committed suicide within two weeks of scoring negative on the eC-SSRS).

3.1.2.8 Rates of psychiatric adverse events in double-blind trials

The sponsor's table below shows the incidence of psychiatric adverse events for all psychiatric events that occurred in 0.1% of brodalumab-treated subjects during 12 weeks of double-blind treatment. Reports of events were generally sparse and similar across treatment groups. Over 12 weeks of treatment, insomnia was the most commonly reported psychiatric event, but no single psychiatric disorder was reported in as many as 1% of subjects. For depression, the rates were 0.5% for brodalumab and 0.6% for placebo (relative risk 0.8, 95% confidence interval 0.3-2.2). Roughly 2% of subjects in all treatment groups reported any type of psychiatric disorder.

Preferred Term	Placebo (N=879) n (%)	Ustekinumab (N=613) n (%)	Brodalumab 140 mg Q2W (N=1491) n (%)	Brodalumab 210 mg Q2W (N=1496) n (%)	Brodalumab All (N=3066) n (%)
Psychiatric disorders	16 (1.8)	12 (2.0)	30 (2.0)	31 (2.1)	61 (2.0)
Insomnia	6 (0.7)	4 (0.7)	7 (0.5)	10 (0.7)	17 (0.6)
Depression	5 (0.6)	3 (0.5)	9 (0.6)	5 (0.3)	14 (0.5)
Anxiety	2 (0.2)	2 (0.3)	10 (0.7)	3 (0.2)	13 (0.4)
Libido decreased	0 (0.0)	0 (0.0)	2 (0.1)	3 (0.2)	5 (0.2)
Depressed mood	1 (0.1)	2 (0.3)	2 (0.1)	1 (0.1)	3 (0.1)
Mood swings	0 (0.0)	0 (0.0)	1 (0.1)	2 (0.1)	3 (0.1)
Stress	1 (0.1)	0 (0.0)	0 (0.0)	3 (0.2)	3 (0.1)

Table 4. Rates of psychiatric adverse events occurring in at least 0.1% of brodalumab subjects in double-blind trials

Source: Table 24, SIB supplement

3.1.2.9 Psychiatric rating scales in clinical trials

<u>Hospital Anxiety and Depression Scale (HADS) in Trial 20120102:</u> The HADS is a 14-item scale, to which the patient responds with a self-rating of 0-3 on 7 symptoms of depression and 7 symptoms of anxiety; it was collected at baseline and Week 12 in Study 20120102 only, and the results showed an imbalance with respect to improved scores. With respect to their baseline depression self-ratings, after 12 weeks 45/60 (75%) of brodalumab-treated subjects improved, compared to 10/22 (46%) of placebo patients. Similarly, on anxiety self-ratings, 67% of brodalumab-treated subjects improved after 12 weeks, versus 8/27 (30%) of placebo-treated subjects.

<u>PHQ-8 depression self-rating scores</u>: As described above, while the trials were ongoing the sponsor implemented screening of subjects for depression with the PHQ-8 scale in response to the concern about suicidality. As noted earlier, a PHQ-8 score ≥ 10 triggered mental health referral, and subjects with a PHQ-8 score ≥ 15 discontinued treatment. The table below shows the incidence of maximum PHQ-8 scores higher than normal (≥ 10), comparing 52 weeks of randomized treatment with either ustekinumab or brodalumab. There was an imbalance in the category of mildly symptomatic maximum ratings, which were more frequent with brodalumab, though rates of higher scores appeared similar between groups. The exposure in patient-years for ustekinumab was roughly 1/6 the exposure for brodalumab, so comparisons should be made cautiously.

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	Ustekinumab	All brodalumab
Maximum	(<i>Pyr</i> =10.3)	(<i>Pyr</i> =60.7)
PHQ-8	(N=78)	(N=474)
Score		n (noto non 100 nom)
(omitting normal scores of 0-4)	n (rate per 100 pyr)	n (rate per 100 pyr)
5 to 9 (mild)	6 (58.3)	68 (112.0)
≥ 10	3 (29.1)	18 (29.7)
\geq 15 (moderately severe to severe)	1 (9.7)	7 (11.5)

Table 5. Maximum higher-than-normal PHQ-8 scores during 52 weeks of treatment withustekinumab or brodalumab (Studies 20120103 and 20120104)

Source: Table 33, SIB supplement. Pyr, patient-year; n, number of subjects with events

3.2 RATES OF SUICIDE BEHAVIOR IN CLINICAL STUDIES OF OTHER PSORIASIS TREATMENTS

3.2.1 Data from Systematic Review of Psoriasis Clinical Studies

In an effort by Amgen to provide a background rate of suicide behavior in psoriasis patients enrolled in clinical trials, Exponent Inc., the consultants to Amgen, conducted a systematic review of phase III and phase IV clinical trials of adult patients with psoriasis and/or psoriatic arthritis treated with biologic agents using literature and publicly available data. Results of the literature review were submitted as part of the Amgen pre-BLA meeting package. The phase III/IV clinical trials of unspecified phase with at least 100 subjects. The studies reviewed included patients treated with the following agents: adalimumab, apremilast, certolizumab pegol, etanercept, golimumab, infliximab, secukinumab, and ustekinumab. Public domain data for ixekizumab or brodalumab were not available, so those agents were not included. For the analysis limited to biologics, presumably apremilast was excluded, though that was not stated explicitly in the submission.

Table 6 presents the incidence of suicide behavior in psoriasis patients treated with the biologics of interest in phase III or IV clinical trials. The incidence rates were reported for all studies combined and were not reported by individual biologic agents. Across 29 studies of psoriasis biologicals with 21,062 total patient-years, there were four completed suicides, yielding a rate of 0.02 per 100 patient-years. Fewer studies supplied data on suicidal ideation or suicide attempts. "Suicide ideation or behavior" occurred at a rate of 0.02 per 100 patient-years although the report failed to specify if suicide behavior referred to suicide attempts, completed suicides or both, and the definition may have varied across studies. The incidence rate of "suicide attempts" was 0.11 per 100 patients-years.

Adverse event	Total Studies	Total Events	Total Patient- Years	Events per 100 Patient- Years	95% Confidence Interval
Completed Suicide	29	4	21,062	0.02	0.01, 0.05
Suicide ideation or behavior	4	2	9,715	0.02	0.002, 0.07
Suicide attempt	3	3	2,675	0.11	0.02, 0.33

 Table 6. Incidence rates of suicidal behavior or ideation among psoriasis

 patients treated with biologics in phase III or IV clinical trials.

ce: Exponent, Inc. report for Amgen, submitted with 5-13-15 pre-BLA meeting materials

Biologics included: adalimumab, certolizumab pegol, etanercept, golimumab, infliximab, secukinumab, and ustekinumab

Sour

3.2.2 Data from Regulatory Submissions

To provide a comparison of data for brodalumab to suicidal adverse event rates previously observed in patients with psoriasis, one of the DEPI reviewers (AM) surveyed data from other regulatory submissions for drugs and biologics in the treatment of psoriasis. From the sources noted in Table 6, the reviewer obtained event counts for suicide, suicide attempt, and (if available) suicidal ideation, with corresponding persontime of exposure and numbers of subjects. The emphasis was on data from psoriasis trials specifically, when the data were available, but in some submissions the sponsor pooled psoriasis trial data with data from trials for other indications. The reviewer included only the data for the compound under development, as the placebo and active comparator groups had limited sample sizes and those data were less informative. Apremilast, a non-biologic agent for the treatment of psoriasis was included because depression and suicidal thoughts are listed in the Warnings and Precautions section of the label. The reviewer calculated crude rates for suicide, attempted suicide, and suicidal ideation, per 100,000 person-years. The reviewer also calculated overall pooled rates, but omitted two compounds that are probable outliers: brodalumab (because it has a signal for suicide), and apremilast (because it has a label warning for depression). It should be mentioned that the sparseness of the data (low event counts) results in imprecise rate estimates. Also, although these rates reflect mostly psoriasis trial data, there was some heterogeneity in the indications studied. Other sources of heterogeneity among the data sources that should be noted include use of the C-CASA adjudication system by some, but not all sponsors, length of follow-up, and differences in subject selection criteria.

The pooled completed suicide rate for other products of 0.02 per 100 patient-years (23.7 per 100,000 patient-years) (four suicides/21,131 patient-years of treatment with six compounds) was in line with the pooled rate from the Exponent Inc., literature review (0.02 per 100 patient-years).

Table 7. Rates of Suicide Behavior in Psoriasis Clinical Trials											
Dataset, indication	Ν	Exposure Patient - years	Completed suicides, N	Suicide Attempts N	Suicides/ 100,000 PY	Attempts/ 100,000 PY	Suicides+ Attempts/ 100,000 PY	Suicidal Ideation, N	Ideation/ 100,000 PY	Adjudicated w/ C-CASA?	
Brodalumab, all indications(1)	6,240	10,438	6**	15	57.5	143.7	201.2	18	172.5	No	
Brodalumab, PsO trials (2)	4,464	7,895	4**	7	50.7	88.7	139.3	18	228	No	
Ixekizumab (3)	4,209	6,480	0	9	0	140	140	0	0	Yes	
Apremilast, PsO, PsA, RA (4)	2,401	1,483	1	2	67.4	134.9	202.3	2	134.9	Yes	
Etanercept, PsO (5)	1,807	2,773	0	1	0	36.1	36.1	2	72.1	No	
Adalimumab, PsO (6)	1,468	4,069	1**	0	24.6	0	24.6	3	73.7	No	
SecukinumabPsO, PsA (7)	3,928	3,225	0*	1	0	31	31	1	31	Yes	
Ustekinumab, PsO (8)	3,117	6,791	1	0	14.7	0	14.7	0	0	No	
Infliximab, PsO safety summary (9)	1,564	1,263	0	3	0	237.5	237.5	0	0	No	
Briakinumab, PsO trials (10)	2,520	3,011	2**	0	66.4	0	66.4	1	33.2	No	
Pooled w/o brodalumab, apremilast	14,404	21,131	4	5	18.9	23.7	42.6	7	33.1		

PY = patient-years 1 Monthly safety report #18

2 Amgen briefing document for 5-13-2015 meeting 3 Lilly Ixekizumab C-CASA report 6/24/2015 4 Celgene Apremilast "C-CASA White Paper"

5 Amgen Etanercept ISS for long-term exposure (12-13-2006)

6 Abbott adalimumab study report (4-14-2010) 7 Novartis secukinumab C-CASA Report

Suicide risk for brodalumab DEPI-I review.doc 3-22-2016

8 Centocor submission (7-6-2011)

9 Centocor submission (8-5-2005) 10 EMA Rapporteurs' Day 80 Critical Assessment Report (12-10-2010) *One subject committed suicide during screening

**Includes suicides during post-treatment follow-up

15

One may compare the suicide rate in the brodalumab trials to the rates observed with the other recently developed IL-17 biologic products for psoriasis. In fact, there were no suicides in subjects receiving ixekizumab or secukinumab in clinical trials, though one prospective subject in a secukinumab trial committed suicide during screening. Accordingly, a relative risk cannot be calculated, but the p-value for the comparison to brodalumab is statistically significant, as shown here.

	Completed Suicides	Suicide attempt/ behavior	Suicides+ Attempts	Subjects	Person-years of exposure
Brodalumab	6	15	21	6,240	10,438
Ixekizumab	0	9	9	4,209	6,480
Secukinumab	0	1	1	3,928	3,225
Ixe+Sec	0	10	10	8,137	9,705
IXE+Sec	0 For Comple	eted suicide,	Brodalumab vs	8,137 s lxe+Sec:	9,705

<u>Observed-to-expected comparison</u>: If we consider the suicide rate observed in Exponent's systematic review of Phase III-IV biologic psoriasis trials (4 suicides in 21,062 person-years, or 0.019 per 100 person-years) as the expected rate, then the observed brodalumab rate (6 suicides in 10,438 person-years, or 0.057 per 100 person-years) is 3-fold higher (relative risk 3.0, 95% CI 0.7-14.6, $p=0.09^{1}$), corresponding to roughly one excess suicide per every 2600 person-years of brodalumab use.

<u>Proportionate mortality analysis:</u> According to the sponsor's SIB 6-Month Cumulative Report #3, through September 30, 2014, there were 32 deaths during brodalumab treatment across all indications, and 6 of these 32 (19%) were suicides. In comparison, according to Exponent's systematic review submitted by Amgen, the all-cause mortality rate in biologics psoriasis trials was 0.207 per 100 person-years, and the suicide rate was 0.019 per 100 person-years, or 9% of the total mortality rate. Thus, the proportion of deaths that were suicides in the brodalumab trials was roughly double what has been observed in previous psoriasis biologics clinical trials. However, this comparison has the limitation of ignoring possible differences in subject characteristics across development programs, with respect to disease severity, age, gender, comorbidities, etc.

4 **DISCUSSION**

The original sponsor discontinued all ongoing brodalumab trials following concerns regarding an apparent excess of SIB events. The crucial question is whether such SIB events could be causally related to brodalumab use. Some thoughts on making this assessment follow.

Meaningful comparisons of brodalumab SIB rates to placebo or active controls are not available from the brodalumab development program, because of the short duration of exposure to those comparators, and the relative infrequency of SIB event. Ordinarily, the data of most inferential value in evaluating such a potential signal would be the comparisons

¹ Stata version 12.0 (StataCorp, College Station, TX)

to placebo or active controls in clinical trials. However, the cumulative exposures to placebo or active controls were insufficient to provide meaningful comparisons of SIB frequency to brodalumab.

Comparisons to external controls indicate an inordinate number of completed suicides in brodalumab clinical trials. Although comparisons to external or historical controls provide a lower quality of evidence than internal comparisons within the same development program, it may be necessary to resort to such comparisons to assess uncommon events. To this end, Amgen provided a systematic review of suicide and other adverse events in psoriasis clinical trials. However, we regarded the data in Amgen's systematic review on completed suicide (from 29 trials) as being more informative for comparisons than the data on suicidal ideation and behavior (which was available from only 4 trials). Also, the data on suicidal ideation and attempts in brodalumab trials was profoundly influenced by implementation of the eC-SSRS, which was not used in other trials.

The rate of suicide in the brodalumab clinical trials was roughly three times higher than expected when compared to clinical trials of other biologics for psoriasis, a difference approaching statistical significance (p=0.09). The excess rate of suicide with brodalumab was roughly one per 2600 person-years of exposure. The proportion of all deaths that were due to suicide in brodalumab clinical trials (19%) was roughly twice the proportion in psoriasis trials of other biologics (9%). With respect to other IL-17 agents, there were no completed suicides among subjects treated with either ixekizumab or secukinumab in clinical trials (though one prospective secukinumab subject committed suicide during screening).

The incidence of suicidal behavior and ideation was likely to have been underestimated prior to use of the eC-SSRS. Ordinarily one would expect that the rate of suicide attempts would be considerably higher than the rate of completed suicide, and the rate of suicidal ideation to be higher still, as was seen in FDA's meta-analysis of antidepressant clinical trials (9). Based on data from the CDC's Web-based Injury Statistics Query and Reporting System (WISQARS), it is estimated that there are 12 attempted suicides for every completed suicide, though that ratio varies by age and gender. The ratio of the suicidal behavior rate to the completed suicide rate was 1.8 before the eC-SSRS, and 5.0 after the eC-SSRS (Table 3), consistent with improved ascertainment of suicide attempts. Thus, implementation of the eC-SSRS monitoring appears to have improved detection of not only suicidal ideation but probably of suicide attempts also.

Though the eC-SSRS improved ascertainment of SIB, the data are not adequate to determine whether the eC-SSRS reduced the rate of attempted or completed suicide. There were not enough events to make meaningful comparisons of rates before and after implementation of the eC-SSRS. While two subjects who committed suicide reported negative eC-SSRS scores shortly before their deaths, intervention may have protected other subjects who gave positive responses.

There does not appear to be a good rationale for separating data on SIB in psoriasis trials from SIB data in other indications. The sponsor's submission emphasizes psoriasis trial data, but for uncommon outcomes the totality of the data should be considered, as there is no obvious reason to assume a risk of SIB would vary substantially by indication.

Evidence suggests a relatively high prevalence of suicidality among patients with rheumatoid arthritis (10) and asthma (11), similar to observations in the psoriasis population.

Data on psychiatric adverse events other than SIB do not suggest a relationship to brodalumab, but the ability to detect adverse mental effects in the trials was probably *limited.* Data from 12-week double blind segments of the trials show sparse numbers of events, with similar rates for brodalumab, ustekinumab and placebo. However, rates for commonly expected psychiatric events such as insomnia and depression appeared relatively low (<1%), raising the possibility that these events were under-ascertained. Consistent with this, from Table 5, the rate of moderate or severe depression with brodalumab in Studies 20120103 and 20120104, defined by the rate of subjects having a maximum PHQ-8 score >9, was 41.2 per 100 patient-years, while in 12-week controlled trials (Table 4), the rate of depression and depressed mood as adverse events with brodalumab was 0.6% (or roughly 2.4 per 100 patient-years). Data from the psychiatric self-report scales were mixed, with the HADS showing more improvement on depression and anxiety symptoms among brodalumab-treated subjects relative to placebo, and the PHQ-8 showing more frequent reports of mild depression with brodalumab than ustekinumab. Though the available data do not delineate a pattern of brodalumab-related mental changes or psychiatric symptoms, this does not rule out a relationship of SIB to brodalumab; there may have been limited capacity to detect such a pattern if there was under-reporting of psychiatric events generally. In addition, depression may present with a suicide attempt; one study of antidepressant users showed they were more likely to have made a suicide attempt immediately before rather than immediately after an antidepressant prescription (12).

Existing pharmacovigilance and pharmacoepidemiology methods will not be adequate to assess the risk of SIB with brodalumab in the post-marketing environment. FAERS data would be insufficient to further asses this risk because of under-reporting of SIB events, and the expected baseline rate of events given the comorbidity of depression with psoriasis. A pharmacoepidemiology study would also be difficult as a recent systematic review highlighted the challenges of studying suicide and suicide attempts in health care claims data settings (e.g., Sentinel) (13). Similar limitations have been noted for studies of suicide and self-harm in the U.K. Clinical Practice Research Datalink (14).

5 CONCLUSIONS

Should the rates observed in trials apply in the postmarketing patient population, there would be roughly one excess suicide per every 2600 person-years of brodalumab use compared to other biologics.

Rates of suicidal behavior that did not result in suicide, and of suicidal ideation, appear to have been under-ascertained prior to monitoring of trial subjects with the eC-SSRS. It is difficult to determine to what degree enhanced detection with the eC-SSRS may have prevented suicidal behaviors.

Brodalumab clinical trial data do not show evidence for other mental effects, but the ability of the clinical monitoring to detect such effects was questionable.

Subjects with a past psychiatric history for depression or SIB had a much higher rate of SIB, though only 2 of the 6 subjects who committed suicide had a positive psychiatric history.

On balance, though a causal relationship of SIB to brodalumab use is uncertain, we conclude there is "insufficient information about the drug to determine whether the product is safe for use" per 21 CRF 314.125(b) (4).

6 **RECOMMENDATIONS**

- 1. Although a causal relationship of SIB to brodalumab use is uncertain, to the extent there is currently "insufficient information about the drug to determine whether the product is safe for use," DDDP and ODE III may need to consider a Complete Response per 21 CRF 313.125(b)(4).
- 2. If brodalumab is approved,
 - a. Restricting its use to patients without a relevant past psychiatric history would serve to reduce the number of SIB events among brodalumab users, even regardless of the extent to which SIB events are causally related.
 - b. Clinical monitoring of users with the eC-SSRS (or perhaps a comparable tool) would greatly improve the chances of detecting SIB, so that patients could be directed to obtain treatment and discontinue brodalumab.
 - c. A REMS could be considered to help implement a) and b) above.
 - d. Appropriate labeling and a Medication Guide would help communicate this issue to prescribers and patients.
 - e. No postmarketing observational data collection would be recommended, given the limitations of such data for suicidal outcomes.

CC:

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APPENDIX A. DESCRIPTIONS OF SUICIDAL IDEATION AND BEHAVIOR CASES IN BRODALUMAB CLINICAL TRIALS

COMPLETED								Time from 1st	Time from last			
SUICIDE							Date of	dose	dose	Past psychiatric	Final eC-SSRS	
Subject ID	Indication	Study	Age	Sex	Treatment	Event	event	(days)	(days)	history	score, date	Comments
					Brodalumab	Suicide by	(b) (6)				
961660001003	RA	20090402	36	F	210 mg	hanging		231	7	Neg	N/A	No premonitory signs per husband. Financial stress.
					Brodalumab	Suicide by						No psychiatric adverse events, no premonitory signs
10248005019	PsO	20120102	59	М	210 mg	hanging		329	58	Neg	N/A	per wife. Financial stressors.
						Death from						Per coroner, death due to toxicity from morphine,
					Brodalumab	overdose on						methadone and EtOH (classified as suicide).
10216004001	PsO	20120102	56	М	210 mg	opioids, EtOH		97	14	Depression	N/A	Investigator felt could have been accidental.
					Brodalumab	Suicide, method						No psychiatric adverse events reported. Facing legal
10366026017	PsO	20120103	39	М	210 mg	not reported		224	27	Neg	N/A	problems and possible incarceration.
					Brodalumab	Suicide by					Neg on	
22766006003	PsA	20101227	57	м	210 mg	firearm		965	41	Neg	9/8/2014	(b) (6)
										Depression, anxiety		
					Brodalumab	Suicide by				(investigator	Neg on	Reportedly experiencing stress from a recent move. C/o
10366026003	PsO	20120103	56	м	210 mg	jumping		845	19	unaware)	2/9/2015	insomnia. Receiving trazodone 100 mg/d.

SUICIDE ATTEMPT							Date of	Time from 1st dose	Time from last dose		Final eC-SSRS		Brodalumab
Subject ID	Indication	Study	Age	Sex	Treatment	Event	event	(days)	(days)	Past psychiatric history	score, date	Comments	d/c?
							(b) (6)		Depression, insomnia.			
					Brodalumab	Overdose on				On venlafaxine,			
96116002001	RA	20090061	42	F	210 mg	lorazepam, alcohol		70	14	lorazepam	N/A	Hospitalized	yes
						Overdose on				Depression, suicidal			
					Brodalumab	Vicodin and				ideation, anxiety,		Concomitant medications included	
10366084033	PsO	20120103	51	М	210 mg	alcohol		26	12	alcohol abuse	N/A	vilazodone, clonazepam	no
						Attempted suicide						Psychiatrically hospitalized, prescribed	
	"	"	"	"	"	with car exhaust		40	12	"	"	escitalopram	no
						Put a gun to his							
	"	"		"	"	head		115	3	"	"	Few details provided	no
10366074008	PsO	20120103	22	F	Ustekinumab	Aspirin overdose							
------------------------	-----	-----------------	----	---	----------------------	---							
10366026018	PsO	20120103	55	м	Brodalumab 210 mg	On railroad track w/suicidal intent							
4827-005-003- TB-03	PsO	KHK4827 (Japan)	63	м	Brodalumab	Cutting on self							
10312006006	PsO	20120103	47	M	Brodalumab 210 mg	Positive eC-SSRS for suicide attempt							
10311001004	PsO	20120103	48	м	Brodalumab 210 mg	Cut wrist (6 cm)							
10429012006	PsO	20120104	51	F	Brodalumab 210 mg	"Preparatory actions for suicidal behavior"							
10325005006	PsO	20120103	45	F	Brodalumab 210 mg	Three "aborted suicide attempts," no further details							
10366064009	PsO	20120103	24	F	Brodalumab 210 mg	Attempted suicide with car exhaust							
10348002066	PsO	20120103	61	F	Brodalumab 210 mg	Overdose of sleeping pills							
10348005021	PsO	20120103	63	F	Brodalumab 210 mg	"Suicidal behavior" per eC-SSRS							
		н	"		п	Positive eC-SSRS for suicidal behavior							
10349002004	PsO	20120103	52	F	Brodalumab 210 mg	Overdose on unspecified pills							
10466074023	PsO	20120104	63	м	Brodalumab 210mg	Positive eC-SSRS for aborted suicide attempt and preparatory actions							

	Suicide	attempts,	continued
--	---------	-----------	-----------

(b)(6)						
(0) (0)			Depression, suicidal			
			ideation, substance			
			abuse, childhood			
	156		abuse	N/A		N/A
			ADHD, depression, in		On methylphenidate, venlafaxine. Stressors:	
			day treatment. No past		denied disability, lost custody of daughter.	
	540	8	suicidality	N/A	Hospitalized.	yes
					While on brodalumab, sought psychiatric	
			Dysthymic disorder		referral for difficulty with anger, diagnosed	
			diagnosed during		with dysthymic disorder, received	
	529	?	treatment	N/A	quetiapine and ramelteon.	yes
			Depression, suicide			
	160	7	attempt	Pos (7) 8/5/2014	No details regarding suicide attempt	yes
					Hospitalized, diagnosed with adjustment	
			Depression, alcohol		d/o, depressed mood, personality d/o.	
	644	9	use	Neg 8/14/2014	Marital issues.	yes
Ĩ			Depression treated			
			with alprazolam,			
	168	7	escitalopram	Pos 10/8/2014	Positive cC-SSRS and PHQ-8, no other details	yes
					Receiving mental health treatment at	
			Anxiety, depression,		enrollment. Timing of aborted suicide	
	644	14	suicide attempt	Pos 12/8/2014	attempts unclear.	ves
			Depression, suicidal		Following suicide attempt, treated as	
	754	16	ideation	Neg, Jan ? 2015	outpatient for depression w/fluoxetine	ves
					Subject disclosed suicide attempt on end-of-	
	282	?	Depression	Pos 4/27/2015	treatment eC-SSRS	ves
				Popost of SSPS		·
	202	2	Negativo	negative	Subject claimed she misunderstood eC-SSPS	VOC
, e	393	:	Negative	negative	Subject claimed she misunderstood ec-55k5	yes
					No dotails regarding suisidal behavior	Noc
			Depression suisidal		Subject reported event retrospectively on	yes
	525	7	Depression, suicidai	Dec 11/7/2014		
, e	525	/	Denavior	POS 11/7/2014	ec-ssks	yes
	c 7 2	2		D C/45/2015		
	6/2	? ?	Depression	Pos 6/15/2015	No details regarding suicide attempt.	yes

									Time				
SUICIDAL								Time from 1ct	from				
IDEATION							Date of	dose	dose		Final eC-SSRS score.		
Subject ID	Indication	Study	Age	Sex	Treatment	Event	event	(days)	(days)	Past psychiatric history	date	Comments	Brodalumab d/c?
					Brodalumab	Suicide	(b) (b)		Depression, alcohol		Subject also had suicide attempt next day on	
10311001004	PsO	20120103	48	М	210 mg	ideation		643	8	use	Neg 8/14/2014	(b) (6)	yes
						Had dreams of							
						killing herslef. Had							
10466024007	D:O	20120104	62	_	Brodalumab	action plan but no		520	22	Anxiety, depression,	Nog 9/26/2014	Taking dapaganam tragodona narovotina	Vac
10406024007	PSU	20120104	62	F	210mg	Positive eC-SSRS		528	22	Schizooffective	Neg 8/26/2014	Taking cionazeparii, trazodone, paroxetine.	yes
					Brodalumab	for chronic suicide				disorder, suicidal			
10216007007	PsO	20120102	54	м	210mg	ideation		625	9	ideation	Pos 7/30/2014		ves
					Brodalumab	Suicide			-	Depressive disorder,		Stopped taking Zoloft on 6/15/2014 and alprazolam on 7/1/2014. Brodalumab was discontinued after 7/4/2014 visit and resumed 8/29/2014. Patient referred to psychiatrist who confirmed that the subject did not have any thoughts of death or	,
10466021025	PsO	20120104	40	F	210mg	ideation in dreams		385	7	panic disorder, PTSD	Neg 8/7/2014	suicidal ideation.	temporarily
14166064007	Asthma	210120141	43	F	Brodalumab 210mg	Positive eC-SSRS for lifetime SIB and 1 actual attempt before enrollment		98	14	Anxiety, depression, suicidal ideation since March 2010	Pos 6/11/2014		yes
10366052004	PsO	20120103	35	м	Brodalumab 140mg	Hospitlaized due to life threatening suicide plan		474	22	Depression, anxiety, alcoholism, suicide ideation, suicide attempt	Pos (18) 6/25/2014	Relationship stress and divorce.	yes
10366043007	PsO	20120103	68	F	Brodalumab 210mg	Hospitalized due to moderate active suicide ideation		322	14	Anxiety, depression	N/A	Financial and family stressors.	yes
10466006002	PrO.	20120104	47		Brodalumab	Suicidal ideation. Did not want to kill himself but he was worried		112	0	Suicide ideation, anxiety, depression, alcohol abuse, bipolar, mood	Nog 5/29/2014	Con meds: olanzapine and fluoxetine. Financial and family stressors. Treatment	tomporarily
10400090003	PSU	20120104	47		ZIOUIB	Suicidal ideas			0	uisoraer.	11eg 5/28/2014	stopped 2/17/2014 and resumed 3/31/2014.	temporarity
10425004004	PsO	20120104	62	м	Ustekinumab	which warranted hospitalization.		181	13	Alcohol abuse	N/A	Family problems that led to depression at the time of the event	yes
10448003070	PsO	20120104	43	м	Brodalumab 210mg	Positive eC-SSRS for suicide ideation		393	43	None	Pos 8/22/2014	Consumed large quantity of alcohol prior to visit with pos eC-SSRS.	yes

Suicidal ideation, continued

							(b) (6)					
						Positive eC-SSRS						No personal stressors. Investigator reported	
						for suicide ideation						that there was a reasonable possibility that	
					Brodalumah	(thinking of cutting						the event of suicidal ideation was related to	
22766004000	DcA	20101227	52	M	210mg	himcolf)		025	15	PTSD dysthymia	Nog 12/15/2014	investigational product	VOC
22700004009	FSA	20101227	33		210111g	minisenj		923	15	FISD, uysuiyinia	Neg 12/ 13/ 2014		yes
										1994, 3 suicide			
										attempts, 2			
										preparatory actions		6/12/2014 subject reported depressive	
						Positive eC-SSRS				prior to study		symptoms over past 1 ½ months due to	
14166074017	Asthma	20120141	43	М	Placebo	for suicide ideation		172	46	enrollment.	Pos (5) 8/7/2014	recent life events (lost job, divorce, stress).	yes
						Positive eC-SSRS							
						for suicide							
						ideation, some							
					Brodalumab	intent to act but							
10225002009	PsO	20120102	63	м	210mg	not plan		616	12	Depression	Pos 10/20/2014.	Financial issues. Con meds: Sertraline	yes
						Positive eC-SSRS							
						for suicide							
						ideation, some							
					Brodalumab	intent to act but				Anxiety, depression,		Receiving mental health treatment at	
10325005006	PsO	20120103	45	F	210 mg	not plan		644	14	suicide attempt	Pos 12/8/2014	enrollment. Family issues.	ves
												,, ,, ,, ,	1
					Brodalumab	Positive eC-SSRS				Depression, suicidal		Subject reported experiencing suicide	
10349002004	PsO	20120103	52	F	210 mg	for suicide ideation		525	7	ideation and behavior	Pos 11/7/2014	ideation retrospectively on eC-SSRS	ves
				-					-				100
					Brodalumah	Positive eC-SSRS				Depression suicide			
10466006020	PsO	20120104	56	F	210mg	for suicide ideation		595	16	ideation	Pos 3/11/2015	Financial issues	ves
1010000020		20120101	50	<u> </u>	2101118	for suicide facation			10	lacation			yes.
						Positive eC-SSRS							
						for lifetime suicide							
					Brodalumah	ideation with come						Einancial issues Subject already receiving	
10249006001	DcO.	20120102	52		210mg	intent but no plan		670	2	2020	Dec (4) 0/20/2014	montal health care at time of of SSRS	200
10248000001	PSU	20120102	52	101	210111g	Suicidal ideation		078	ſ	none	POS (4) 9/29/2014	mental health care at time of ec-33K3.	yes
						diagneeed by							
					Due de la consta	diagnosed by						No information for this subject in the CID	
400000000000					Brodalumab	physician at			2			No information for this subject in the SIB	
10366023009	PsO	20120103	59	M	210mg	hospital		569	?	Alcohol abuse	Neg (date unknown)	supplement.	yes
						Positive eC-SSRS						Relationship stress.Con meds: citalopram,	
1				1		tor aborted suicide						bupropion hydrochloride, zolpidem tartrate,	
					Brodalumab	attempts,				Depression, insomnia,		trazodone. No informaiton for this subjecy	
10466052008	PsO	20120104	66	М	210mg	preparatory actions		314	?	suicide ideation	Pos 6/15/2015	in the SIB supplement.	yes
												No information for this subject in the SIB	
												supplement.On 9/17/2015 visit subject	
					Brodalumab	Positive eC-SSRS						reported they were no longer feeling	
96211901012	PsO	20090403	46	м	dose?	for severe ideation		1770	?	None	Neg 9/17/2015	suicidal.	?

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

/s/

GABRIELLA M ANIC 03/22/2016

ANDREW D MOSHOLDER 03/22/2016

SUKHMINDER K SANDHU 03/22/2016

SIMONE P PINHEIRO 03/22/2016

RPM FILING REVIEW

(Including Memo of Filing Meeting)

To be completed for all new NDAs, BLAs, and Efficacy Supplements [except SE8 (labeling change with clinical data) and SE9 (manufacturing change with clinical data]

Application Information							
NDA # NA	NDA Supplement #	#: S- NA	Efficacy Supplement Category:				
BLA# 761032	BLA Supplement #	#: S- NA	New Indication (SE1)				
			New Dosing Regimen (SE2)				
			New Route Of Administration (SE3)				
			Comparative Efficacy Claim (SE4)				
			New Patient Population (SE5)				
			Rx To OTC Switch (SE6)				
			Accelerated Approval Confirmatory Study				
			(SE7)				
			Labeling Change With Clinical Data (SE8)				
			Manufacturing Change With Clinical Data				
			Animal Rule Confirmatory Study (SE10)				
Proprietary Name: IBD	1 1 1 1						
Established/Proper Name:	brodalumab						
Dosage Form: for injection	1						
Strengths: 210 mg							
Applicant: AstraZeneca	1° 11 \ \ \						
Agent for Applicant (if app	licable): NA						
Date of Application: 16-N	ov-15						
Date of Receipt: 16-Nov-1	5						
Date clock started after UN	: NA						
PDUFA/BsUFA Goal Date	: 16-Nov-16	Action Goal D	Date (if different): 02-Nov-16				
Filing Date: 15-Jan-16		Date of Filing	Meeting: 05-Jan-16				
Chemical Classification (or	riginal NDAs only) :						
Type 1- New Molecular E	ntity (NME); NME an	d New Combinat	ion				
Type 2- New Active Ingre	edient; New Active Ing	redient and New	Dosage Form; New Active Ingredient and New				
	NDF						
Type 3- New Dosage Forr	n; New Dosage Form a	and New Combin	ation				
Type 4- New Combination							
Type 5- New Formulation	or New Manufacturer						
Type /- Drug Already Ma	rketed without Approv	ved NDA					
Type 8- Partial Rx to OIC		41 4 4 4					
Proposed indication(s)/Prop	posed change(s): For	the treatment	of adult patients with moderate to				
severe plaque psoriasis w	ho are candidates	for systemic th	erapy or phototherapy				
Type of Original NDA			505(h)(1)				
AND (if applicable	.)		$\Box 505(0)(1)$				
Turna of NDA Symplows anti-	5)		505(0)(2)				
Type of NDA Supplement.			$\Box 505(0)(1)$				
If 505(h)(2). Draft the "505(1	() Assessment" row	ew found at					
http://inside.fda.gov:9003/CDER/Of	ficeofNewDrugs/Immediate	Office/UCM027499.					

Type of BLA			51(a) 51(k)				
If 351(k), notify the OND Therapeutic Bio	ologics and Biosimilars Te	eam					
Review Classification:			$ \square S$ $ \square P$	tandard riority			
The application will be a priority review if							
• A complete response to a pediatri	c Written Request (WR) w	'as	Р	ediatric	WR		
included (a partial response to a	WR that is sufficient to ch	ange	🗖 ç	IDP			
the labeling should also be a prio	rity review – check with L	PPMH)	🗍 T	ropical	Disease Priority		
• The product is a Qualified Infect	ious Disease Product (QII	DP)	Revie	wVouc	her		
A Iropical Disease Priority Revie	w Voucher was submitted	! :44 - J	🗌 P	ediatric	Rare Disease Priority		
A Pediatric Kare Disease Priority	Keview voucner was sub	miliea	Revie	w Vouc	her		
Resubmission after withdrawal? Resubmission				fuse to f	ile?		
Part 3 Combination Product? Convenience kit/Co-pa Pre-filled drug delivery Pre-filled biologic delivery Pre-filled biologic delivery Device coated/impregn Device coated/impregn 				backage ry device/system (syringe, patch, etc.) livery device/system (syringe, patch, etc.) gnated/combined with drug			
	auiring	cross-la	abeling				
	.1						
	n based	on cros	ss-label	ing of separate			
	Other (drug/device/	biologica	al produ	uct)			
 Fast Track Designation Breakthrough Therapy Designation (set the submission property in DARRTS and notify the CDER Breakthrough Therapy Program Manager) Rolling Review Orphan Designation Rx-to-OTC switch, Full Rx-to-OTC switch, Partial Direct-to-OTC Other: 	05(o)] rred ped d approv R 601.4 e postma ety (21 0	iatric s val con 1) urketing CFR 31	tudies (firmato g studie: 4.610/2	FDCA Section ry studies (21 CFR s to verify clinical 21 CFR 601.42)			
Collaborative Review Division (if OTC	<i>product</i>): NA						
List referenced IND Number(s): 10467	71						
Goal Dates/Product Names/Classi	fication Properties	YES	NO	NA	Comment		
PDUFA/BsUFA and Action Goal dates correct in tracking system?							
If no, ask the document room staff to correct them immediately. These are the dates used for calculating inspection dates.							
Are the established/proper and applicant names correct in tracking system?					Applicant name incorrect. Emailed DR to correct on 11/18		
ask the document room staff to make ask the document room staff to add the est to the supporting IND(s) if not already ent	e ine corrections. Also, tablished/proper name tered into tracking						

Version: 7/10/2015

NO	NA	Comment			
_	_				
NO	NA	Comment			
is appli	cation (a	check daily email from			
<u>/serFeeAR@fda.hhs.gov</u>):					
\square Paid					
Exempt (orphan, government)					
g., smal	l busine	ss, public health)			
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avment of other user fees:					
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	ing poli	by been appropriately			
n you a	a e not sl	ne, consult the User			
-					
		Comment			
NO	NA	Comment			
	NA	Comment			
	NO N	NO NA NO NA NO NA Image: Second Se			

Version: 7/10/2015

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questions below:					
• Is the application for a duplicate of a listed drug and					
eligible for approval under section 505(j) as an ANDA?					
• 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)].					
• 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)]?					
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					
Ja there upowpired evolucivity on erether listed dress					
• Is there unexpired exclusivity on another listed drug					
product containing the same active molety (e.g., 5-year,					
3-year, orphan, or pediatric exclusivity)?					
Check the Electronic Orange Book at: http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm					
If ves. please list below:					
Application No. Drug Name Exclusivity Co	ode	Exc	usivity	Expiration	
				1	
If there is unexpired, 5-year exclusivity remaining on another listed a	lrug prod	uct cont	aining t	he same activ	e moiety,
a $505(b)(2)$ application cannot be submitted until the period of exclu	sivity exp	ires (un	less the d	applicant prov	vides
paragraph IV patent certification; then an application can be submit	ted four y	ears aft	er the do	ate of approva	ıl.)
Pediatric exclusivity will extend both of the timeframes in this provis	ion by 6 n	nonths.	21 CFR	314.108(b)(2)).
Unexpired, 3-year exclusivity may block the approval but not the sub	mission o	of a 505(b)(2) ap	plication.	
Exclusivity	YES	NO	NA	Comment	t
Does another product (same active moiety) have orphan					
exclusivity for the same indication? <i>Check the Orphan Drug</i>					
Designations and Approvals list at:					
http://www.accessdata.fda.gov/scripts/opdlisting/oopd/index.cfm					
In another product has orphan exclusivity, is the product					
drug definition of someness [see 21 CED 216 3(b)(12)]?					
If yes, consult the Director, Division of Regulatory Policy II					
Office of Regulatory Policy					
NDAS/NDA efficacy supplements only: Has the applicant					
NDAs/NDA efficacy supplements only: Has the applicant requested 5-year or 3-year Waxman-Hatch exclusivity?					
NDAs/NDA efficacy supplements only: Has the applicant requested 5-year or 3-year Waxman-Hatch exclusivity?					
NDAs/NDA efficacy supplements only: Has the applicant requested 5-year or 3-year Waxman-Hatch exclusivity? If yes , # years requested:					
NDAs/NDA efficacy supplements only: Has the applicant requested 5-year or 3-year Waxman-Hatch exclusivity? If yes, # years requested:					
 NDAs/NDA efficacy supplements only: Has the applicant requested 5-year or 3-year Waxman-Hatch exclusivity? If yes, # years requested: Note: An applicant can receive exclusivity without requesting it; 					

NDAs only : Is the proposed product a single enantiomer of a racemic drug previously approved for a different therapeutic		
use?		
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)?		
If yes, contact the Orange Book Staff (CDER-Orange Book Staff).		
BLAs only: Has the applicant requested 12-year exclusivity under section 351(k)(7) of the PHS Act?		Emailed on 11/18
If yes, notify Marlene Schultz-DePalo, CDER Purple Book Manager		
<i>Note:</i> 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		
exclusivity is not required.		

Format and Co	ontent					
Do not check mixed submission if the only electronic component is the content of labeling (COL).	 All paper (except for COL) All electronic Mixed (paper/electronic) 					
	CTD Non-CTD Mixed (C) TD/noi	n-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).						
Index: Does the submission contain an accurate comprehensive index?						
Is the submission complete as required under 21 CFR 314.50 (<i>NDAs/NDA efficacy supplements</i>) or under 21 CFR 601.2 (<i>BLAs/BLA efficacy supplements</i>) including:						

1

http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072349. pdf

English (or translated into English)				
\square English (of translated into English)				
\square pagination pag				
That igable hyperinks (electronic submissions only)				
If no, explain.				
BLAs only: Companion application received if a shared or				
divided manufacturing arrangement?				
If yes, BLA #				
Forms and Certifications				
<i>Electronic</i> forms and certifications with electronic signatures (sca	nned, digital, o	r electro	nic – sir	nilar to DARRTS, e.g.,
/s/) are acceptable. Otherwise, paper forms and certifications with	hand-written s	ignature	s must k	pe included.
Forms include: user fee cover sheet (3397/3792), application form	n (356h), patent	informa	tion (35	542a), financial
disclosure (3454/3455), and clinical trials (3674); Certifications i	include: debarm	ent certi	ification	, patent
<i>certification(s), field copy certification, and pediatric certification</i>		NO		a
Application Form	YES	NO	NA	Comment
Is form FDA 356h included with authorized signature per				
21 CFR 314.50(a)?				
If foreign applicant a U.S. agent must sign the form [see 2]				
CFR 314.50(a)(5)].				
Are all establishments and their registration numbers listed				
on the form/attached to the form?				
Patent Information	YES	NO	NA	Comment
(NDAs/NDA efficacy supplements only)				
Is patent information submitted on form FDA 3542a per 21				
CFR 314.53(c)?				
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)?				
Forms must be signed by the ADDI ICANT not an Agent [see				
21 CFR 54 2(g)]				
21 OI R 52(8)].				
<i>Note:</i> Financial disclosure is required for bioequivalence studies				
that and the hagin for annuoual				
inal are the basis for approval.		-		
Clinical Trials Database	YES	NO	NA	Comment
Clinical Trials Database Is form FDA 3674 included with authorized signature?	YES	NO	NA	Comment
Clinical Trials Database Is form FDA 3674 included with authorized signature?	YES 🛛	NO	NA	Comment
Index of the basis for approval. Clinical Trials Database Is form FDA 3674 included with authorized signature? If yes, ensure that the application is also coded with the	YES	NO	NA	Comment
Indicate the basis for approval. Clinical Trials Database Is form FDA 3674 included with authorized signature? If yes, ensure that the application is also coded with the supporting document category, "Form 3674."	YES		NA	Comment

If no, ensure that language requesting submission of the form is included in the acknowledgement letter sent to the applicant				
Debarment Certification	YES	NO	NA	Comment
Is a correctly worded Debarment Certification included with authorized signature?				
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].				
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"				
Field Copy Certification (NDAs/NDA efficacy supplements only)	YES	NO	NA	Comment
For paper submissions only: Is a Field Copy Certification (that it is a true copy of the CMC technical section) included?				
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)				
If maroon field copy jackets from foreign applicants are received, return them to CDR for delivery to the appropriate field office.				
Controlled Substance/Product with Abuse Potential	YES	NO	NA	Comment
For NMEs: Is an Abuse Liability Assessment, including a proposal for scheduling, submitted per 21 CFR 314.50(d)(5)(vii)?				
If yes, date consult sent to the Controlled Substance Staff:				
For non-NMEs: Date of consult sent to Controlled Substance Staff:				
Pediatrics	YES	NO	NA	Comment
Does the application trigger PREA?				
If yes, notify PeRC@fda.hhs.gov to schedule required PeRC meeting ²				

²

 $[\]underline{http://inside~fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/PediatricandMaternalHealthStaff/uc}{m027829~htm}$

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.				
If the application triggers PREA , is there an agreed Initial Pediatric Study Plan (iPSP)?				
If no, may be an RTF issue - contact DPMH for advice.				
If required by the agreed iPSP, are the pediatric studies outlined in the agreed iPSP completed and included in the application?				Agreed iPSP granted partial waiver 0 to 6 and deferral 6 - 17 y/o
If no, may be an KIF issue - contact DPMH for advice.		_		
BPCA: Is this submission a complete response to a pediatric Written Request?				
If yes, notify Pediatric Exclusivity Board RPM (pediatric exclusivity determination is required) ³				
Proprietary Name	YES	NO	NA	Comment
Is a proposed proprietary name submitted?	\square			
If yes, ensure that the application is also coded with the supporting document category, "Proprietary Name/Request for Review."				
REMS	YES	NO	NA	Comment
Is a REMS submitted?	\square			
If yes, send consult to OSE/DRISK and notify OC/ OSI/DSC/PMSB via the CDER OSI RMP mailbox				
Prescription Labeling	Not app	plicable		
Check all types of labeling submitted.	 Package Insert (PI) Patient Package Insert (PPI) Instructions for Use (IFU) Medication Guide (MedGuide) Carton labels Immediate container labels Diluent Other (specify) 			(PPI) FU) dGuide)
	Immedi	ate contains specify)	ainer la	bels
	Carton I Immedi Diluent Other (s	ate conta specify)	ainer la	Comment
Is Electronic Content of Labeling (COL) submitted in SPL format?	Carton	ate conta specify) NO	ainer la	bels Comment

³

 $[\]underline{http://inside~fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/PediatricandMaternalHealthStaff/uc}{m027837~htm}$

Is the PI submitted in PLR format? ⁴				
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? If no waiver or deferral, request applicant to submit labeling in				
PLR format before the filing date.				
For applications submitted on or after June 30, 2015: Is the PI submitted in PLLR format? ⁵				
Has a review of the available pregnancy and lactation data been included?				
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? <i>If no waiver or deferral, request applicant to submit labeling in</i> <i>PLR/PLLR format before the filing date.</i>				
All labeling (PI, PPI, MedGuide, IFU, carton and immediate container labels) consulted to OPDP?				
MedGuide, PPI, IFU (plus PI) consulted to OSE/DRISK? (send WORD version if available)				
Carton and immediate container labels, PI, PPI sent to OSE/DMEPA and appropriate CMC review office in OPQ (OBP or ONDP)?				
OTC Labeling	Not App	olicable	è	·
Check all types of labeling submitted.	Not App Outer carton label Immediate container label Blister card Blister backing			

4

 $[\]underline{http://inside~fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/StudyEndpointsandLabelingDevelopmentTeam/ucm025576~htm}$

http://inside_fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/StudyEndpointsandLabelingDevelopmentTeam/ucm025576 htm

	Consumer			
	Information			
	Leaflet			
	(CIL)			
	Physician			
	sample			
	Consumer			
	consumer			
	(specify)			
Is electronic content of labeling (COL) submitted?	YES	NO	NA	Comment
If no, request in 74-day letter.				
Are annotated specifications submitted for all stock				
keeping units (SKUs)?				
If no, request in 74-day letter.				
If representative labeling is submitted, are all represented				
SKUs defined?				
If no, request in 74-day letter.				
All labeling/packaging sent to OSE/DMEPA?				
Other Consults				
Are additional consults needed? (e.g., IFU to CDRH; QT	YES	NO	NA	Comment
study report to QT Interdisciplinary Review Team)				
If yes, specify consult(s) and date(s) sent:				
Meeting Minutes/SPAs				
End-of Phase 2 meeting(s)?	YES	NO	NA	Comment
Date(s):				
If yes, distribute minutes before filing meeting				
Pre-NDA/Pre-BLA/Pre-Supplement meeting(s)?				
Date(s): January 21, March 25, and October 21, 2015;				
If yes, distribute minutes before filing meeting				
Any Special Protocol Assessments (SPAs)?				
Date(s):				
If yes, distribute letter and/or relevant minutes before filing				
meeting				

ATTACHMENT

MEMO OF FILING MEETING

DATE: January 5, 2016

BACKGROUND: brodalumab is a IL-17a receptor inhibitor, for the treatment of adult patients with moderate to severe plaque psoriasis who are candidates for systemic therapy or phototherapy. The filing date is January 15, 2016, 74 day letter date is January 29, 2016 amd the PDUFA date is November 16, 2016.

REVIEW TEAM:

Discipline/Organization		Names	Present at filing meeting? (Y or N)
Regulatory Project Management	RPM:	Strother D. Dixon	Y
	CPMS/TL:	Barbara Gould	N
Cross-Discipline Team Leader (CDTL)	David Kettl	MD	Y
Division Director/Deputy	Kendall A.	Marcus, MD	Y
Office Director/Deputy	Julie Beitz,	MD	Y
Clinical	Reviewer:	Gary Chiang, MD	Y
	TL:	David Kettl, MD	Y
Clinical Pharmacology	Reviewer:	Jie Wang, PhD	Y
	TL:	Yow-Ming Wang, PhD	N
Genomics	Reviewer:	NA	NA
Pharmacometrics	Reviewer:	Dhananjay Marathe, PhD	Y
Biostatistics	Reviewer:	Carin Kim, PhD	Y
	TL:	Mohamed Alosh, PhD	Y
Nonclinical (Pharmacology/Toxicology)	Reviewer:	Carmen Booker, PhD	Y
	TL:	Barbara Hill, PhD	Y
Statistics (carcinogenicity)	Reviewer:	NA	NA
	TL:	NA	NA

Product Quality (CMC) Review Team:	ATL:	Joanna Zhou, PhD	Y
	RBPM:	Andrew Shiber	Ν
Drug Substance	Reviewer:	Willie Wilson, PhD	Y
Drug Product	Reviewer:	NA	NA
• Process	Reviewer:	Maria Jose Lopez- Barragan, PhD	Ν
	TL:	Reyes Candau-Chacon, PhD	Y
Microbiology	Reviewer:	NA	NA
• Facility	Reviewer:	Don Obenhuber, PhD	Ν
Biopharmaceutics	Reviewer:	NA	NA
Immunogenicity	Reviewer:	NA	NA
• Labeling (BLAs only)	Reviewer:	Jibril Abdus-Samad, PhD	Ν
• Other (e.g., Branch Chiefs, EA Reviewer)	NA		NA
OMP/OMPI/DMPP (Patient labeling: MG, PPI, IFU)	Reviewer:	Rowell Medina, PharmD	Y
	TL:	Barbara Fuller, PharmD	NA
OMP/OPDP (PI, PPI, MedGuide, IFU, carton and immediate container labels)	Reviewer:	Tara Turner, PharmD, MPH	NA
	TL:	Melinda McLawhom, PharmD	NA
OSE/DMEPA (proprietary name, carton/container labels)	Reviewer:	Carlos Mena-Grillasca, RPh	Y
	TL:	Mishale Mistry, PharmD	NA
OSE/DRISK (REMS)	Reviewer:	Jasminder (Jessy) Kumar, PharmD, RPh	Y
	TL:	Jamie Wilkins-Parker, PharmD	Y
OC/OSI/DSC/PMSB (REMS)	Reviewer:		
	TL:		

Bioresearch Monitoring (OSI)	Reviewer:	Roy Blay, PhD	Y
	TL:	NA	NA
Controlled Substance Staff (CSS)	Reviewer:	NA	NA
	TL:	NA	NA
Other reviewers/disciplines			
ODE III *For additional lines, highlight this group of cells,	Deputy Director:	Amy Egan, MD, ODE III	Y
copy, then paste: select "insert as new rows"	ADRA:	Maria Walsh, RN, MS	Y
	Regulatory Scientist:	LCDR Richard Ishihara	Y
• DDDP *For additional lines, highlight this group of cells, copy, then paste: select "insert as new rows"	Deputy Director for Safety:	Tatiana Oussova, MD	Y
	Associate Director for Labeling:	Nancy Xu, MD	Y
	Sr. RPM:	Matthew White	Y
• DPMH	Reviewer:	Christos Mastroyannis, MD	Y
	TL:	Tamara Johnson, MD MS	Y
	Sr. RPM	Matthew Bacho	Y
• DEPI	Reviewer:	Gabriella Anic, PhD, MPH, Regulatory Review Officer, DEPI	Y
	Medical Officer:	Andy Mosholder, MD, MPH	Y
	TL:	LCDR Sukhminder K. Sandhu, PhD, MPH, MS	Y
	ORISE Fellow:	Richard Swain	Y
• DBVII	Lead Mathematical Statistician:	Clara Kim, PhD	Y
	Statistician	Ling Lan, PhD	Y
• DPV	Acting Director, DPV I	Robert L. Levin, MD	Y
	TL, DPV I	Ida-Lina Diak, PharmD,	Y
	Safety	Jessica Weintraub,	Y

Version: 7/10/2015

	Evaluator	PharmD, BCPS,	
Division of AC and	Senior	Jennifer Shepherd	Y
Consultant Management	Regulatory	_	
	Sr.	Yvette Waples	Y
	Supervisory		
	Regulatory:		
CDRH/ODE/GHDB	Reviewer:	Janice Ferguson, RN,	Y
		BSN, CRNI	
Other attendees	Sarah Kennett, I	PhD, Review Chief, DMA	Y
	Hae Young Ahn, PhD, DCPIII		Y
	Louis Flower, Sr. Program		Y
	Management,		
	Ephrem Hunde	e, Chemical Engineer,	Y
	Inspectional A	ssessment Branch III	

FILING MEETING DISCUSSION:

GENERAL	
• 505(b)(2) filing issues:	Not Applicable
 Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA? 	□ YES □ NO
 Did the applicant provide a scientific "bridge" demonstrating the relationship between the proposed product and the referenced product(s)/published literature? 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): 	UYES NO
• Per reviewers, are all parts in English or English translation?	∑ YES □ NO
If no, explain:	
Electronic Submission comments	☐ Not Applicable☑ No comments
List comments:	

CLINICAL	Not Applicable
	REFUSE TO FILE
Comments:	Review issues for 74-day letter
• Clinical study site(s) inspections(s) needed?	YES NO
If no, explain:	
Advisory Committee Meeting needed?	YES
Comments:	Date if known: NO To be determined
If no, for an NME NDA or original BLA, include the reason. For example:	Reason: suicides/suicide ideation associated with BLA 761032 brodalumab
disease	
• 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?	 ☑ Not Applicable ☑ YES ☑ NO
Comments:	
 CONTROLLED SUBSTANCE STAFF Abuse Liability/Potential 	 Not Applicable FILE REFUSE TO FILE
Comments:	Review issues for 74-day letter
CLINICAL MICROBIOLOGY	 Not Applicable FILE REFUSE TO FILE
Comments:	Review issues for 74-day letter

CLINICAL PHARMACOLOGY	Not Applicable
	FILE
	REFUSE TO FILE
Comments : Comments to convey in an IR prior to sending the 74-day letter.	Review issues for 74-day letter
• Clinical pharmacology study site(s) inspections(s)	YES
needed?	NO NO
BIOSTATISTICS	Not Applicable
	FILE
	REFUSE TO FILE
Comments:	Review issues for /4-day letter
NONCLINICAL (BHADMACOLOCY/TOXICOLOCY)	Not Applicable
(PHARMACOLOGI/IOAICOLOGI)	$\square REFLISE TO FILE$
	Review issues for 74-day letter
Comments:	
PRODUCT OUALITY (CMC)	Not Applicable
	FILE
	REFUSE TO FILE
	Bayion issues for 74 day letter
Comments:	
New Molecular Entity (NDAs only)	
• Is the product an NME?	
• Is the product an initial?	I I I I I I I I I I I I I I I I I I I
Environmental Assessment	
Categorical exclusion for environmental assessment	X YES
(EA) requested?	
If no, was a complete EA submitted?	
Commente	
Comments.	
Facility Inspection	Not Applicable
 Establishment(s) ready for inspection? 	VFS
• Establishment(s) ready for hispection?	NO
Comments:	

Version: 7/10/2015

Facility/Microbiology Review (BLAs only)	Not Applicable
	FILE FILE
	REFUSE TO FILE
Comments:	Review issues for 74-day letter
CMC Labeling Review (BLAs only)	
Comments:	Review issues for 74-day letter
APPLICATIONS IN THE PROGRAM (PDUFA V) (NME NDAs/Original BLAs)	N/A
• 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?	⊠ YES □ NO
• If so, were the late submission components all submitted within 30 days?	⊠ YES □ NO
• What late submission components, if any, arrived after 30 days?	 Stability Data Update Proprietary Name Review
• Was the application otherwise complete upon submission, including those applications where there were no agreements regarding late submission components?	⊠ YES □ NO
• Is a comprehensive and readily located list of all clinical sites included or referenced in the application?	⊠ YES □ NO
• Is a comprehensive and readily located list of all manufacturing facilities included or referenced in the application?	⊠ YES □ NO

REGULATORY PROJECT MANAGEMENT				
Signatory Authority: Julie Beitz, MD				
Date of Mid-Cycle Meeting (for NME NDAs/BLAs in "the Program" PDUFA V): April 6, 2016				
21 st Century Review Milestones (see attached) (listing review milestones in this document is optional):				
Comments:				
REGULATORY CONCLUSIONS/DEFICIENCIES				
	The application is unsuitable for filing. Explain why:			
	The application, on its face, appears to be suitable for filing.			
	Review Issues:			
	 No review issues have been identified for the 74-day letter. Review issues have been identified for the 74-day letter. 			
	Review Classification:			
	Standard Review Priority Review			
ACTION ITEMS				
	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).			
	If RTF, notify everyone who already received a consult request, OSE PM, and RBPM			
	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.			
	If priority review, notify applicant in writing by day 60 (see CST for choices)			
	Send review issues/no review issues by day 74			
	Conduct a PLR format labeling review and include labeling issues in the 74-day letter			
	Update the PDUFA V DARRTS page (for applications in the Program)			
	Other			

Annual review of template by OND ADRAs completed: September 2014

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

/s/

STROTHER D DIXON 01/12/2016

BARBARA J GOULD 01/12/2016

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

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

Application: BLA 761032

Application Type: New BLA

Drug Name(s)/Dosage Form(s): brodalumab injection, 210 mg

Applicant: AstraZeneca UK Ltd

Receipt Date: November 16, 2015

Goal Date: November 16, 2016

1. Regulatory History and Applicant's Main Proposals

BLA 761032 brodalumab is a new BLA submitted under PDUFA V. BLA 761032 brodalumab is an IL-17a receptor inhibitor, for the treatment of adult patients with moderate to severe plaque psoriasis who are candidates for systemic therapy or phototherapy. The clinical studies were completed under IND 104671.

2. Review of the Prescribing Information

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

3. Conclusions/Recommendations

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

4. Selected Requirements of Prescribing Information

The Selected Requirement of Prescribing Information (SRPI) is a 41-item, drop-down checklist of important <u>format</u> 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 ¹/₂ inch margins on all sides and between columns.

Comment:

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

Comment:

- YES 3. A horizontal line must separate:
 - HL from the Table of Contents (TOC), and
 - TOC from the Full Prescribing Information (FPI). *Comment:*
- YES 4. All headings in HL (from Recent Major Changes to Use in Specific Populations) must be **bolded** and presented in the center of a horizontal line. (Each horizontal line should extend over the entire width of the column.) The HL headings (from Recent Major Changes to Use in Specific Populations) should be in UPPER CASE letters. See Appendix for HL format.

Comment:

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

Comment:

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

Comment:

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

Heading	Required/Optional
 Highlights Heading 	Required
 Highlights Limitation Statement 	Required

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

* RMC only applies to <u>five</u> 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. <u>Comment</u>:

Highlights Limitation Statement

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

Product Title in Highlights

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

Comment:

Initial U.S. Approval in Highlights

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

Comment:

Boxed Warning (BW) in Highlights

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

Comment:

N/A
 13. The BW must have a title in UPPER CASE, following the word "WARNING" and other words to identify the subject of the warning. Even if there is more than one warning, the term "WARNING" and not "WARNINGS" should be used. For example: "WARNING: SERIOUS

INFECTIONS and ACUTE HEPATIC FAILURE". If there is more than one warning in the BW title, the word "and" in lower case can separate the warnings. The BW title should be centered.

Comment:

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

Comment:

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

Comment:

Recent Major Changes (RMC) in Highlights

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

Comment:

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

Comment:

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

Comment:

Dosage Forms and Strengths in Highlights

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

Comment:

Contraindications in Highlights

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

Comment:

Adverse Reactions in Highlights

YES 21. For drug products other than vaccines, the verbatim **bolded** statement must be present: "To report SUSPECTED ADVERSE REACTIONS, contact (insert name of manufacturer) at

(insert manufacturer's U.S. phone number which should be a toll-free number) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch."

Comment:

Patient Counseling Information Statement in Highlights

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

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

• 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 <u>Comment</u>:

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: XX/XXXX is currently in the label as a placeholder. The RPM will update at the time of approval.

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.

<u>Comment</u>:

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)].

<u>Comment</u>:

YES 29. The section and subsection headings in the TOC must match the section and subsection headings in the FPI.

<u>Comment</u>:

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:

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 <u>section</u> (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:

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

N/A 37. If no Contraindications are known, this section must state "None."

Comment:

ADVERSE REACTIONS Section in the FPI

YES 38. When clinical trials adverse reactions data are included (typically in the "Clinical Trials Experience" subsection), the following verbatim statement (<u>or appropriate modification</u>) 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:

PATIENT COUNSELING INFORMATION Section in the FPI

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

Comment:

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

Comment:

Appendix: Highlights and Table of Contents Format

HIGHLIGHTS OF PRESCRIBING INFORMATION -----DOSAGE FORMS AND STRENGTHS------These highlights do not include all the information needed to use Dosage form(s): strength(s) (3) PROPRIETARY NAME safely and effectively. See full prescribing information for PROPRIETARY NAME. -----CONTRAINDICATIONS------ Text (4) PROPRIETARY NAME (non-proprietary name) dosage form, route Text (4) of administration, controlled substance symbol Initial U.S. Approval: YYYY -----WARNINGS AND PRECAUTIONS------ Text (5.x) WARNING: TITLE OF WARNING Text (5.x) See full prescribing information for complete boxed warning. -----ADVERSE REACTIONS------ Text (4) Most common adverse reactions (incidence > x%) are text (6.x) Text (5.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. -----RECENT MAJOR CHANGES------Section Title, Subsection Title (x.x) M/201Y -----DRUG INTERACTIONS------Section Title, Subsection Title (x.x) M/201Y Text (7.x) Text (7.x) -----INDICATIONS AND USAGE------PROPRIETARY NAME is a (insert FDA established pharmacologic -----USE IN SPECIFIC POPULATIONS-----class text phrase) indicated for ... (1) Text (8.x) Text (8.x) Limitations of Use: Text (1) See 17 for PATIENT COUNSELING INFORMATION and -----DOSAGE AND ADMINISTRATION-----FDA-approved patient labeling OR and Medication Guide. Text (2.x) Text (2.x) 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/

STROTHER D DIXON 01/12/2016

BARBARA J GOULD 01/12/2016