

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

761032Orig1s000

**RISK ASSESSMENT and RISK MITIGATION
REVIEW(S)**

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
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Review Completion Date	February 15, 2017
Subject	Review of REMS Proposal
Established Name	Brodalumab
Applicant	Valeant Pharmaceuticals
Application Number	BLA 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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Executive Summary

This review by the Division of Risk Management (DRISK) evaluates whether a risk evaluation and mitigation strategy (REMS) for the new molecular entity (NME) Siliq (brodalumab), a 351(a) biologic, is necessary to ensure the benefits of the product outweigh the risks.

AstraZeneca submitted a Biologic Licensing Application (BLA 761032) for brodalumab on November 16, 2015, for the treatment of adult patients with moderate to severe plaque psoriasis who are candidates for systemic therapy or phototherapy. Ownership of the BLA was subsequently transferred to Valeant Pharmaceuticals (Valeant) on April 1, 2016. The major risks associated with the use of brodalumab are suicidal ideation and behavior (SIB), infections, Crohn's disease, immunosuppression, and hypersensitivity events. The Applicant's original BLA submission included a proposed REMS that consisted of a Medication Guide (MG), communication plan (CP), and a 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 due to the risk of Crohn's disease; and to educate patients to recognize the signs and symptoms of SIB or changes in their mental health, and to seek intervention should such signs emerge.

DRISK and the Division of Dermatology and Dental Products (DDDP) as well as senior-level management in CDER did not agree with the Applicant's original proposal, but instead determined that a REMS with elements to assure safe use (ETASU) is needed to ensure the benefits of brodalumab outweigh the risk of suicidal ideation and behavior. The REMS required elements include health care providers who prescribe the drug are specially certified (ETASU A), pharmacies that dispense the drug are specially certified (ETASU B), and the drug be dispensed only to patients with evidence or other documentation of safe-use conditions (ETASU D) to ensure that prescribers and patients are informed about the risk of SIB observed with brodalumab therapy.

On August 22, 2016, the Applicant was informed of our determination that a REMS that includes ETASU was necessary. The Agency provided guidance on what was necessary for the REMS document, materials, and supporting document; and these were subsequently discussed between the Agency and Valeant by email communications, meetings, and teleconferences. On February 13, 2017, Valeant submitted an amended REMS proposal that consists of ETASU (prescriber certification, pharmacy certification, and documentation of safe-use conditions), an implementation system; and a timetable for submission of assessments. DRISK finds the submission acceptable; therefore, DRISK recommends approval of the REMS submitted on February 13, 2017.

1 Introduction

This review by the Division of Risk Management (DRISK) evaluates whether a risk evaluation and mitigation strategy (REMS) for the new molecular entity (NME) Siliq (brodalumab) is necessary to ensure the benefits of this product outweigh its risks. AstraZeneca submitted a Biologic Licensing Application (BLA) 761032 for brodalumab on November 16, 2015, for the proposed indication of treatment of adult patients with moderate to severe plaque psoriasis who are candidates for systemic therapy or phototherapy. This application is under review in the Division of Dermatology and Dental Products (DDDP). The Applicant's original BLA submission proposed a REMS consisting of a Medication Guide, communication plan (CP), and a 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 due to the risk of Crohn's disease; and to educate patients to recognize the signs and symptoms of SIB or changes in their mental health, and to seek intervention should such signs emerge. Ownership of the application was subsequently transferred from AstraZeneca to Valeant on April 1, 2016.

DRISK and the Division of Dermatology and Dental Products (DDDP) as well as senior-level management in CDER did not agree with the Applicant's original proposal, but agreed that a REMS with elements to assure safe use (ETASU) is needed to ensure the benefits of brodalumab outweigh the risk of suicidal ideation and behavior. The REMS required elements include health care providers who prescribe the drug are specially certified (ETASU A), pharmacies that dispense the drug are specially certified (ETASU B), and the drug be dispensed only to patients with evidence or other documentation of safe-use conditions (ETASU D) to ensure that prescribers and patients are informed about the risk of SIB observed with brodalumab therapy. The REMS goal is to mitigate the observed risk of suicidal ideation and behavior, including completed suicides, which occurred in subjects treated with SILIQ by 1) ensuring that prescribers are educated about the risk of suicidal ideation and behavior observed with SILIQ therapy and the need to counsel patients about this risk; and 2) ensuring that patients are informed about the risk of suicidal ideation and behavior observed with SILIQ therapy and the need to seek medical attention for manifestations of suicidal thoughts and behavior, new onset or worsening depression, anxiety, or other mood changes.

On August 22, 2016, the Applicant was informed of our determination that a REMS that includes ETASU was necessary. The Agency provided guidance on what was necessary for the REMS document, materials, and supporting document; this was subsequently discussed between the Agency and Valeant by email communications, meetings, and teleconferences. On February 13, 2017, Valeant submitted an amended REMS proposal that consists of ETASU (prescriber certification, pharmacy certification, and documentation of safe-use conditions); an implementation system; and a timetable for submission of assessments. DRISK finds the submission acceptable; therefore, DRISK recommends approval of the REMS submitted on February 13, 2017.

2 Background

2.1 PRODUCT INFORMATION

Brodalumab, a new molecular entity,^a 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 brodalumab 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 brodalumab concentrations for 95% of subjects would drop below the limit of detection approximately 32 days and 63 days after discontinuing treatment with brodalumab 140 mg Q2W and 210 mg Q2W, respectively.

The proposed mechanism of action of brodalumab 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 for the treatment of adults with moderate to severe plaque psoriasis who are candidates for systemic therapy or phototherapy. The ixekizumab product labeling includes warnings and precautions for infections, tuberculosis, hypersensitivity reactions, inflammatory bowel disease, and immunizations, but does not include a boxed warning and did not require a REMS to ensure the benefits outweigh the risks of ixekizumab.

On July 4, 2016, the Japanese Authority approved brodalumab for marketing. 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 which, at the time of this review, is still currently under consideration.

2.2 REGULATORY HISTORY

The following is a summary of the regulatory history for BLA 761032 relevant to this review:

5/30/2013: The Applicant submitted an IND Adverse Event Report to IND 104671, notifying the Agency of the first report of a completed suicide in a patient taking brodalumab.

2/7/2014: Amgen submitted an IND Adverse Event Report to IND 104671 regarding potential risk of suicidal ideation and behavior (SIB), based on safety monitoring, which included a total of 11 SIB events, including 4 completed suicides and 3 deaths from unknown causes. It was determined that all 11 subjects with SIB events were taking active drug, including 2 subjects exhibiting SIB in the ustekinumab arm.

^aFDAAA factor (F): Whether the drug is a new molecular entity.

3/26/2014: A teleconference was convened between Amgen and the Agency, to discuss Amgen's action plan (i.e., details of the plan, timeline, and actions already taken) in response to the SIB report.

3/25/2015: A pre-BLA meeting was held between the Agency and the Applicant. The Agency informed the Applicant that depression and suicide ideation would be a focused review issue and recommended additional discussion with the Agency about this safety signal and risk mitigation, prior to BLA submission.

5/13/2015: A Type C meeting was held, during which the Agency met with Amgen to discuss the completed suicides and SIB observed in the clinical development program for brodalumab. The Agency recommended the Applicant further evaluate this risk and propose a robust risk mitigation program, in order to minimize this safety concern, at the time of BLA submission.

5/22/2015: Amgen announced the company commenced termination of its participation in the co-development of brodalumab with AstraZeneca, and initiated a plan for early termination of all ongoing clinical trials across all indications.

9/1/2015: Valeant entered into a collaboration agreement with AstraZeneca under which Valeant has an exclusive license to develop and commercialize brodalumab globally, except in Japan and certain other Asian countries where rights are held by Kyowa Hakko Kirin Co., Ltd.

10/21/2015: A pre-BLA meeting was held between the Agency and the Applicant. The Applicant was informed that the need for a REMS will be determined during review of the application.

11/16/2015: 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 due to the risk of Crohn's disease; and to educate patients to recognize the signs and symptoms of SIB or changes in their mental health, and to seek intervention should such signs emerge.

4/1/2016: Ownership of BLA 761032 was transferred from AstraZeneca to Valeant Pharmaceuticals, North America LLC.

4/20/2016: 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.

6/28/2016: 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 Advisory Committee meeting on July 19, 2016. The Agency informed Valeant that discussion of risk management options is ongoing.

7/19/2016: 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.

8/22/2016: Valeant was informed during a teleconference with DRISK and DDDP that optimized labeling and a REMS with ETASU is required for brodalumab. Valeant was asked to submit a timeline for the submission of their revised REMS.

8/26/2016: Valeant requested a meeting with DRISK and DDDP to further discuss the Agency's labeling and REMS requirements.

8/31/2016: 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.

9/16/2016: 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.

9/28/2016: Valeant requested a face-to-face meeting with the Agency to discuss labeling and the REMS.

10/5/2016: A meeting was held between the Agency and Valeant. Valeant also invited Dr. Mark Lebwohl, a dermatologist who had participated in the brodalumab clinical program, to discuss the Agency's REMS requirements. Valeant said they were still considering the Agency's requirements.

10/18/2016: Valeant submitted an amendment to their REMS proposal.

10/25/2016: 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.

12/13/2016: 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.

12/16/2016: 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.

12/22/2016: Valeant submitted a REMS amendment to BLA 761032; the submission included the REMS materials omitted from the Applicant's December 16, 2016 submission; however, it did not include a REMS document and REMS supporting document.

12/23/2016: The Agency emailed comments to the Applicant based on the Applicant's December 16, 2016 submission. The Agency advised the Applicant that patient enrollment is necessary to support ETASU D, and that an implementation system is necessary to monitor and evaluate the implementation of ETASUs B and D. The Applicant responded to the Agency's comments later the same day, confirming their agreement with the Agency, and agreed to revise their proposed REMS to include the necessary elements.

1/10/2017: The Agency provided comments to the Applicant and the Agency's redlined REMS document, based on the REMS amendments submitted on December 16 and December 22, 2016. The Agency advised the Applicant that significant revisions to the REMS document and REMS appended materials were necessary in order to be acceptable to the Agency.

1/17/2017: Valeant submitted a REMS amendment to BLA 761032 in response to the Agency's January 12, 2017 comments; the submission was incomplete as it did not include the REMS website screenshots.

1/18/2017: The Agency requested a teleconference with the Applicant, to discuss the necessary REMS revisions.

1/23/2017: A teleconference was held between the Agency and Valeant to discuss the Applicant's amended REMS proposal and the Agency's revisions. Valeant confirmed their agreement with the Agency's revisions.

1/23/2017: Valeant submitted their revised REMS patient wallet card for Agency review.

1/24/2017: Valeant submitted REMS correspondence via e-mail to request clarification on the Agency's most recent comments and redlined REMS materials.

1/25/2017: A teleconference was held between the Agency and the Substance Abuse and Mental Health Services Administration (SAMHSA) to discuss the Agency's plan to include reference to the National Suicide Prevention Lifeline in the Siliq labeling and REMS materials.

1/26/2017: The Agency provided Valeant with comments and redlined REMS materials in response to Valeant's January 24, 2017 REMS correspondence. The Agency requested that Valeant revise their materials and resubmit the REMS amendment.

1/31/2017: The Agency provided Valeant with the Agency's redlined prescriber enrollment form via e-mail communication.

2/3/2017: Valeant submitted a REMS amendment to BLA 761032 in response to the Agency's January 26 and 31, 2017 comments.

2/7/2017: The Agency provided comments to the Applicant and the Agency's redlined REMS materials, in response to the Applicant's February 3, 2017 REMS correspondence.

2/9/2017: Valeant submitted REMS correspondence via e-mail, to ask for the Agency's concurrence on Valeant's proposed revisions to the REMS goals and a question about submission of the revised website screenshots.

2/9/2017: The Agency provided comments based on the REMS correspondence submitted February 9, 2017, notifying Valeant that their revised REMS goals are acceptable and additional revisions are necessary to align the REMS materials with the most recent iteration of the labeling. The Agency recommended Valeant wait to resubmit their REMS proposal until the final website screenshots can be included in the submission.

2/10/2017: Valeant submitted a REMS amendment to BLA 761032 based on the Agency's February 9, 2017 comments. Based on review of Valeant's February 10, 2017 submission, the Agency provided comments to the Applicant and the Agency's redlined prescriber enrollment form via e-mail communication sent later that same day.

2/13/2017: Valeant submitted a REMS amendment to BLA 761032 in response to the Agency's February 10, 2017 comments.

3 Therapeutic Context and Treatment Options

3.1 DESCRIPTION OF THE MEDICAL CONDITION

Psoriasis is a common, chronic, inflammatory, multi-system disease with predominantly skin and joint manifestations. It can present in many different patterns from the scalp to the feet and cause psychiatric distress and physical disabilities. Psoriasis affects approximately 2–3% of the U.S. population. It can begin at any age, but one population study of the age of onset revealed two peaks, at age 16 and at age 60. Risk factors may include family history, obesity, smoking and environmental smoke, and heavy alcohol use. Risk factors that may trigger or exacerbate psoriasis include stress, physical trauma to the skin, cold dry weather, sun exposure and hot weather, infections, and certain medications. Moderate to severe psoriasis is a serious and, at times, disabling condition that has a substantial impact on patients' lives.

3.2 DESCRIPTION OF CURRENT TREATMENT OPTIONS

Currently approved drugs for the treatment of moderate to severe psoriasis include the anti-metabolite methotrexate (MTX), tumor necrosis factor (TNF) inhibitors, such as etanercept, adalimumab and infliximab, IL-12+23 antagonist ustekinumab, IL-17A antagonists secukinumab and ixekizumab, T-cell inhibitor cyclosporine (CSA), retinoid acitretin and phosphodiesterase-4 (PDE-4) inhibitor apremilast (See Table 1). Phototherapy, either PUVA (UVA light combined with the psoralen methoxsalen) or UVB light therapy, is also a standard of care treatment for moderate to severe psoriasis patients. The efficacy of these products is generally measured on the Psoriasis Area and Severity Index (PASI), with the change from baseline as the most common

primary efficacy endpoint. The PASI 75 (75% reduction in the PASI score compared to baseline) for currently available drug therapies varies from highly efficacious (PASI 75 \geq 70%) for cyclosporine, infliximab, adalimumab, ustekinumab and secukinumab, to moderately efficacious (PASI 75 \geq 40%) for methotrexate and etanercept, to somewhat efficacious (PASI 75 \geq 20%) for acitretin and apremilast.^b

Table 1: Drugs FDA Approved for the Treatment of Plaque Psoriasis

Drug	Topical	Oral	Injectable
Acitretin		✓	
Adalimumab			✓
Apremilast		✓	
Calcipotriene	✓		
Calcipotriene/betamethasone dipropionate	✓		
Calcitriol	✓		
Cyclosporine		✓	
Desoximetasone		✓	
Dexamethasone sodium phosphate			✓
Etanercept			✓
Infliximab			✓
Ixekizumab			✓
Methotrexate		✓	✓
Methylprednisolone		✓	✓
Tazarotene	✓		
Triamcinolone hexacetonide			✓
Ustekinumab			✓

Infliximab, etanercept, and adalimumab were all approved with a REMS which consisted of a Medication Guide (MG) and communication plan (CP) to address the risks of infections and malignancies. The CP REMS for all three drugs were released from their REMS requirements in 2011 because the CP activities were complete and the REMS assessments demonstrated that the REMS goals were being met. The MG remains a part of the labeling for each of these drugs.

The ustekinumab REMS was approved in 2009 with a REMS with a MG, CP, and timetable for submission of assessments, to address the risks of serious infections, malignancy, and reversible posterior leukoencephalopathy syndrome. In May 2012, a modification was approved to remove the MG from the REMS; the MG remains a part of the labeling.

The most recently approved product for the treatment of moderate to severe psoriasis, ixekizumab, was approved March 22, 2016 without a REMS. All of the approved products for the treatment of moderate to severe psoriasis have significant risks; and there is room for both

^b Liedtka J. DDDP. Clinical Review for Ixekizumab, BLA 125521, dated November 20, 2015.

more efficacious and potentially safer treatment options.^{c,d}

4 Benefit Assessment

The Applicant sought to establish psoriasis efficacy results with three randomized, double-blind, multicenter, placebo-controlled pivotal studies (Trials 102, 103, and 104) conducted in adult subjects with moderate to severe plaque psoriasis (PsO). All three studies included a placebo-controlled 12-week induction phase, 52-week double-blind duration, and open-label long-term extension with an overall duration of up to 271 weeks (approximately 5 years). For all three studies, there was a re-randomization at Week 12. Trial 102 included a withdrawal and retreatment phase. Trials 103 and 104 included an active comparator (ustekinumab) arm during the induction and maintenance phases.

Across the three trials, the primary efficacy endpoints were identical for the placebo-controlled induction phase, and included the proportion of subjects achieving a static Physician Global Assessment (sPGA) score of 0 (clear) or 1 (minimal) at Week 12, and the proportion of subjects achieving a $\geq 75\%$ improvement in Psoriasis Area and Severity Index (PASI) 75 from baseline at Week 12. The PASI 100 (completely clear skin) at Week 12 was used as the primary endpoint for comparisons against ustekinumab and also served as a key secondary endpoint in the placebo comparisons.

The induction phase of all three studies included the same two dosages of brodalumab administered by subcutaneous (SC) injection [210 mg every 2 weeks (Q2W) and 140 mg Q2W]. Trial 102 included a total of 661 psoriasis subjects. The primary endpoints were evaluated at Week 12 and subjects were re-randomized 1:1 to either continue the brodalumab dose that they received in the induction period or switch to placebo. Subjects that continued to receive brodalumab had higher sPGA 0 or 1 response rates at Week 52 (83% and 70% for brodalumab 210 mg Q2W and 140 mg Q2W, respectively), compared to those subjects re-randomized to placebo (0% and 5%, respectively).

Trials 103 and 104 evaluated a total of 1831 and 1881 psoriasis subjects, respectively. These studies included an ustekinumab comparator arm and were similar to each other in design. The maintenance phase included 4 dosages of brodalumab administered SC [210 mg Q2W, 140 mg Q2W, 140 mg every 4 weeks (Q4W), and 140 mg every 8 weeks (Q8W)]. For the comparison of brodalumab against ustekinumab, both brodalumab 210 mg and the weight-based brodalumab dose (210 mg for subjects > 100 kg, and 140 mg for subjects ≤ 100 kg) were superior to

^c Usatine, Richard P., et al. "Chapter 152. Psoriasis." *The Color Atlas of Family Medicine*, 2e. Eds. Richard P. Usatine, et al. New York, NY: McGraw-Hill, 2013. n. pag. AccessMedicine. Web. 6 Oct. 2015.

<http://accessmedicine.mhmedical.com/content.aspx?bookid=685&Sectionid=45361214>.

^d Liedtka J. DDDP. Clinical Review for Ixekizumab, BLA 125521, dated November 20, 2015.

ustekinumab ($p < 0.001$) for the primary endpoint of PASI 100 at Week 12; however, according to the biostatistics reviewer,^e the efficacy analysis for comparing brodalumab 140 mg against ustekinumab was not statistically significant ($p = 0.078$) for PASI 100 at Week 12 in Trial 103.

According to the clinical reviewer, the results of all three pivotal trials (Trials 102, 103, and 104) demonstrate that both brodalumab doses were superior to placebo ($p < 0.001$) for the co-primary endpoints (PASI 75 and sPGA of 0 or 1 at Week 12) as well as the secondary endpoints [PASI 100, sPGA of 0, and Psoriasis Symptom Inventory (PSI) responder at Week 12]. For the comparison of brodalumab against ustekinumab, the brodalumab 210 mg dose was superior to ustekinumab ($p < 0.001$) for the primary endpoint of PASI 100 at Week 12. Overall, the proportion of subjects that maintained their sPGA response was higher for subjects who received brodalumab 210 mg Q2W compared to brodalumab 140 mg doses (Q2W, Q4W, and Q8W) and placebo.^f

Supportive efficacy, safety, and pharmacokinetic data was provided from Trial 062, a randomized, double-blind, placebo-controlled, dose-finding Phase 2 PsO study, which included 198 subjects, and its open-label extension, Trial 403, which included 184 subjects.

5 Risk Assessment & Safe-Use Conditions

The total safety population ($n = 5205$) for brodalumab was populated by the data from one double-blind, placebo-controlled Phase 2 psoriasis study (Trial 062), its open-label extension study (Trial 403), and three pivotal Phase 3 placebo-controlled trials, two of which were also ustekinumab-controlled. The safety population included 4461 psoriasis subjects who received at least one dose of brodalumab during Phase 2 or 3 of the clinical program, for a combined total of 8655 patient-years of exposure. Importantly, due to the Applicant's early termination of all trials following reports of suicidal ideation and behavior in study subjects, the limited drug exposure for brodalumab is considered by the clinical reviewer to be less than adequate to fully assess the risk of SIB. Of the 4461 psoriasis subjects exposed to at least one 140 mg dose of brodalumab, 1304 were exposed for at least one year on the proposed dosing regimen. The most important adverse events (AEs) associated with the use of brodalumab appear to be suicidal ideation and behavior (SIB), serious infections, tuberculosis, and Crohn's disease.

The overall exposure-adjusted rate of serious adverse events (SAE) was 7.4% in the all-brodalumab psoriasis group. The incidence of subjects with SAEs by treatment arm is shown in Table 2.

^e Lan L. Division of Biostatistics-VII, Consultative Review of Brodalumab (BLA 761032), July 6, 2016.

^f Chiang G., Division of Dermatology and Dental Products. Clinical Review for Brodalumab, BLA 761032, August 25, 2016.

Table 2. Incidence (%) of Subjects with Serious Adverse Events (SAEs)

Study	Placebo	Brodalumab 140 mg Q2W	Brodalumab 210 mg Q2W	Ustekinumab
Trial 102	1.4	2.7	1.8	N/A
Trial 103	2.6	2.1	1.0	1.3
Trial 104	1.0	1.6	1.4	0.6

The SAEs reported by more than 1 subject were carcinoma (metastatic carcinoma of the small intestine in one subject and basal cell carcinoma in one subject), gastroenteritis, appendicitis, cellulitis, and pancreatitis. The system organ classes (SOCs) with the highest exposure-adjusted SAE rates (per 100 subject years) in the all-brodalumab group were “Infections and Infestations” (1.1); “Cardiac Disorders” (0.9); and “Injury, Poisoning, and Procedural Complications” (0.9).

Of the 23 deaths that occurred in brodalumab-treated patients, 13 were cardiovascular-related causes, including myocardial infarction (4), sudden death/cardiac arrest (3), cerebrovascular accident (2), and other single events (4). The potential risk of MACE was evaluated, and was determined not to be related to the study drug.^{g,h}

5.1 SUICIDAL IDEATION AND BEHAVIOR (SIB)

For purposes of this review, suicidal ideation and behavior (SIB) is defined as a completed suicide, a suicide attempt, or a suicide behavior and suicide ideation.

On May 30, 2013, the Applicant (Amgen) notified the Agency of the first report of a completed suicide in a patient taking brodalumab. On February 7, 2014, Amgen submitted an IND Adverse Event Report to IND 104671 regarding the potential risk of SIB, based on safety monitoring, which included a total of 11 SIB events, including 4 completed suicides and 3 deaths from unknown causes. It was determined that all 11 subjects with SIB events were taking active drug, including 2 subjects exhibiting SIB in the ustekinumab arm.

In response to the SIB report, discussions were held between the Agency and Amgen to discuss Amgen’s plan to address this potential safety signal. DDDP requested consultative review from the Division of Psychiatric Products (DPP) to review and comment on the Applicant’s proposed suicide behavior monitoring plan. The DPP reviewerⁱ and DDDP found the Applicant’s proposed plan acceptable. Subsequent discussions between the Agency and Amgen concluded with an agreement that Amgen would implement the following changes to the brodalumab clinical program:

^g Chiang G. Division of Dermatology and Dental Products. Clinical Review for Brodalumab, BLA 761032, August 25, 2016.

^h Meeting of the FDA Dermatologic and Ophthalmic Drugs Advisory Committee, July 19, 2016, Draft Transcript.

ⁱ Alfaro C. Division of Psychiatry Products, Consultative Review and Evaluation of Clinical Data, dated July 25, 2014.

- Update the Investigator’s Brochure and informed consent documents; and re-consent all subjects
- Amend the exclusion criteria of all ongoing study protocols with the following:
 - Subject has a history or evidence of suicidal ideation (severity level 4 or 5) or any suicidal behavior based on an assessment with the electronic Columbia Suicide Severity Rating Scale (eC-SSRS) at screening and baseline.
 - Subject has a history of major psychiatric disorder such as schizophrenia, other psychotic disorder, or major depression or has a history of substance abuse or any other mental health disorder that, in the opinion of the investigator, would pose a risk to subject safety or interfere with study evaluation, procedures, or completion.
 - Subject has evidence of severe depression based on a total score ≥ 10 on the Patient Health Questionnaire-8 (PHQ-8) at screening or baseline.
- Administer two self-rated scales, the eC-SSRS and PHQ-8, at every visit; subjects identified as at-risk will have investigational product discontinued and will immediately be referred to a mental health professional
- The Applicant will provide regular reports to the Agency regarding depression and SIB using expanded search methodology
- The brodalumab clinical trials independent Data Monitoring Committee will provide paper progress reports to the Agency directly
- The Applicant will perform a quantitative analysis of suicide signals, including analyses of specific and related events in comparison to the control groups

Cumulatively, through September 30, 2015 (termination of the clinical studies), there were a total of 39 SIB events in 34 subjects, with 6 completed suicides (4 in the psoriasis program, one in the rheumatoid arthritis program, and one in the psoriatic arthritis program). There were 12 suicide attempts in 8 subjects; 6 suicidal behaviors in 6 subjects; and 20 suicidal ideations in 18 subjects; which led to the early discontinuation of all brodalumab trials across all indications.

Following submission of the original BLA, DDDP consulted other divisions within the Agency to analyze the data supplied by the brodalumab psoriasis trials including. The Division of Biostatistics-VII (DB-7) reviewer concluded that, in total, 35 SIB events occurred in 4464 brodalumab users, resulting in an incidence of 0.78% (95% CI: 0.63–1.25) and the follow-up time-adjusted incidence rate was 0.38 per 100 subject-years (95% CI: 0.27–0.53). Notably, the subgroup analysis of SIB incidence rate by history of suicidality resulted in a 12- to 18-fold increase among subjects with history compared to those without.^j

To enable a more comprehensive review of the potential risk of SIB, DDDP asked the Division of Epidemiology-I (DEPI-I) to compare the data on SIB in the brodalumab trials to data on SIB

^j Lan L. Division of Biostatistics-VII, Consultative Review of Brodalumab, dated July 6, 2016.

events observed in clinical development programs for other psoriasis biologics. Based on available data, the DEPI-I reviewers concluded that, although a causal relationship of SIB to brodalumab use is uncertain, the comparisons indicate an inordinate number of completed suicides in brodalumab clinical trials. DEPI-I calculated a rate of suicide in patients taking brodalumab (all indications) of 58 per 100,000 patient-years (PY), which is 3-4 times higher than the rate of suicide in clinical trials of other biologics.^k Of note, in the United States in 2013, the reported rate of completed suicides was 12.6 per 100,000 patient-years, and approximately 9.3 million adults (3.9% of the adult U.S. population) reported having suicidal thoughts in the past year.^l The DEPI reviewers added that there is insufficient information about the drug at this time to determine whether the product is safe for use; if brodalumab is approved, the risk of SIB observed in subjects treated with SILIQ should be communicated in the labeling and Medication Guide. The DEPI-I reviewers also concluded that further risk mitigation measures for brodalumab could include restricting its use to patients without a relevant past psychiatric history and clinical monitoring with the eC-SSRS or a similar tool, which may greatly improve the detection of SIB, so that patients could be directed to obtain treatment for SIB and discontinue brodalumab. A REMS could be utilized to help implement both of these strategies.

The Division of Pharmacovigilance (DPV) analyzed all neuropsychiatric adverse event data from the 12-week, placebo-controlled phases of the brodalumab psoriasis studies, as well as the maintenance and long-term, open-label phases of the studies. The DPV reviewer recommended that brodalumab be reserved as a second-line treatment as well as consideration of risk mitigation strategies to address the potential risk of SIB.^m

The brodalumab safety concerns were presented to the FDA Dermatologic and Ophthalmic Drugs Advisory Committee (AC) on July 19, 2016. The majority of the committee agreed that clinicians and patients need to be made aware of the possibility of the risk of SIB. The AC unanimously agreed that brodalumab should be approved. Fourteen committee members voted for the addition of risk management options beyond labeling to mitigate SIB; of those 14, the majority supported a registry of some type.

During the brodalumab clinical trials, the PHQ-8 and eC-SSRS were used to screen for and exclude patients with signs or symptoms or a history of psychiatric disease, which may increase their risk of SIB. According to the DEPI reviewer, however, though these screening tools

^k Mosholder AD, Anic G. DEPI-I Review. Risk of suicide in patients treated with brodalumab BLA 761032. March 22, 2016.

^l Centers for Disease Control and Prevention (CDC). Web-based Injury Statistics Query and Reporting System (WISQARS) [Online]. (2013, 2011) National Center for Injury Prevention and Control, CDC (producer). Available from <http://www.cdc.gov/injury/wisqars/index.html>.

^m Chiang G., Division of Dermatology and Dental Products. Clinical Review for Brodalumab, BLA 761032, August 25, 2016.

improved ascertainment of SIB, the data are not adequate to determine whether the eC-SSRS reduced the rate of attempted or completed suicide. The reviewer added that the ability to detect adverse mental effects in the trials was probably limited.ⁿ

The proposed labeling for brodalumab is currently under review. If approved, brodalumab will be 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. The product label will include a boxed warning and a warning and precaution for the risk of SIB, and states that patients with new or worsening symptoms of depression or suicidality should be referred to a mental health professional, as appropriate. Because of the observed suicidal ideation and behavior in subjects treated with brodalumab, if an adequate response has not been achieved within 12 to 16 weeks, the proposed labeling recommends the prescriber consider discontinuing therapy. Prior to initiating treatment, prescribers should carefully consider the risks and benefits of brodalumab to patients with a history of depression and/or suicidal ideation or behavior. Of note, the proposed labeling includes a 1-page Medication Guide to communicate to patients the serious risks of SIB and serious infections.

5.2 CROHN'S DISEASE

Brodalumab was evaluated in 2 studies of patients with Crohn's disease, both of which were terminated early due to lack of efficacy and safety concerns related to worsening of disease. Since worsening of Crohn's disease in patients with a history of or active Crohn's disease is an important identified risk for brodalumab, patients with a known history of Crohn's disease were excluded from the brodalumab psoriasis trials. The proposed labeling includes a Contraindication for the use of brodalumab in patients with Crohn's disease as well as a Warning and Precaution that advises the discontinuation of brodalumab if the patient develops Crohn's disease while taking brodalumab.

6 Analysis of Expected Post-Market Use

Based on its safety profile, the use of brodalumab will be indicated for patients who have failed to respond or have lost response to other systemic therapies for the treatment of moderate to severe plaque psoriasis. For this reason, we anticipate that the likely prescribers of brodalumab will be dermatologists. The dispensing of brodalumab, which will be packaged as a single-dose prefilled syringe for subcutaneous injection (b) (4), could be performed by any outpatient or inpatient pharmacy, and it is expected that this product would be self-administered by patients or administered to patients by caregivers in the home setting.

ⁿ Mosholder, A. and Anic, G. DEPI-I. Consultative Review of Brodalumab Clinical Trial Data, BLA 761032, March 22, 2016.

It is difficult to predict how frequently patients will follow-up with the prescriber. If patients are tolerating and responding well to treatment, the frequency of their follow-up office visits may be expected to be reduced.

Dermatologists will be the likely prescribers of brodalumab and should have experience with other systemic therapies for psoriasis, including other IL-17-targeted therapies as well as other biologics that have severe toxicities and serious adverse events. It is important that both prescribers and patients are aware of the risk of suicidal ideation and behavior.

7 Risk Management Activities Proposed by the Applicant

The Applicant's original BLA submission included a REMS consisting of a Medication Guide, communication plan (CP), and timetable for submission of assessments. The proposed REMS goals were to inform healthcare providers about the potential risk of SIB in patients with psoriasis and the importance of proper patient selection due to the risk of Crohn's disease; and to educate patients to recognize the signs and symptoms of SIB or changes in their mental health, and to seek intervention should such signs emerge. The Applicant's initial proposed product labeling included a contraindication (Section 4) for use in patients with active Crohn's disease as well as a warning and precaution (Section 5.5) to exercise caution when prescribing brodalumab to patients with a history of Crohn's disease and to discontinue the drug if the patient develops Crohn's disease while taking brodalumab.

7.1 OTHER PROPOSED RISK MANAGEMENT ACTIVITIES

In addition to the Applicant's proposed REMS and routine pharmacovigilance practices, the Applicant has proposed an enhanced pharmacovigilance plan (EPVP) that includes enhanced monitoring, data collection, and data analysis for the following Applicant-identified adverse events of special interest (AESI): SIB, MACE, infections, Crohn's disease, neutropenia, hypersensitivity reactions, and malignancies.

8 DRISK Rationale for a REMS

The brodalumab safety concerns were presented to the FDA Dermatologic and Ophthalmic Drugs Advisory Committee/Drug Safety and Risk Management Advisory Committee (AC) on July 19, 2016. The majority of the committee members agreed that clinicians and patients need made aware of the risk of SIB. The AC unanimously agreed that brodalumab should be approved. Fourteen committee members voted for the addition of risk management options beyond labeling to mitigate SIB; of those 14, the majority supported a registry of some type.

The safety concerns, specifically SIB, were discussed on May 25, 2016 (prior to the AC) and August 9, 2016 at meetings of the REMS Oversight Committee (ROC).^o The ROC recommended that additional risk mitigation measures beyond labeling, including a REMS with elements to assure safe use (ETASU), is necessary to ensure the benefits of brodalumab outweigh the serious risk of suicidal ideation and behavior (SIB), including completed suicides. Labeling alone will not ensure that prescribers and patients are informed of the risk of SIB. AREMS will help ensure that both the prescriber and the patient are informed about the risk of SIB. The REMS will be used to communicate that patients with new or worsening symptoms of depression or suicidality should be referred to a mental health professional, as appropriate.

The minimum necessary elements required to assure safe use include:

1. Prescriber certification to ensure that each prescriber is informed of the risk of SIB and the need to inform patients about this risk;
2. A safe-use condition that each patient, prior to starting brodalumab, is informed about the risk of SIB by completing a patient-prescriber agreement form; and
3. Pharmacy certification to ensure that each pharmacy that dispenses a brodalumab prescription does so only after verifying that the prescriber is certified in the REMS program and the patient has completed a patient-prescriber agreement form.

Further detail on the rationale for the construct of the REMS follows in Section 9.

9 Review of the Applicant's Proposed REMS

After several exchanges between the Agency and Valeant, including a face-to-face meeting, Valeant submitted an amendment to their REMS proposal on October 18, 2016. The Agency, since that time, has provided comments to Valeant on December 13, 2016 and January 12, 23, 26, and 31, and February 7, 9, and 10, 2017; resulting in additional amendments on December 16 and 22, 2016, and January 17, 19, 20, and 24, and February 3, 10, and 13, 2017. The subject of this evaluation is the amendment received on February 13, 2017.

9.1 REMS GOALS

The proposed REMS goal is to mitigate the observed risk of suicidal ideation and behavior, including completed suicides, which occurred in subjects treated with SILIQ by:

- Ensuring that prescribers are educated about the 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 risk of suicidal ideation and behavior

^o As per the 21st Century review process, all REMS with elements to assure safe use (ETASU) are discussed at the REMS Oversight Committee (ROC) which consists of senior-level management from the Offices of New Drugs, Surveillance and Epidemiology, and Regulatory Policy

observed with SILIQ therapy and the need to seek medical attention for manifestations of suicidal thoughts and behavior, new onset or worsening depression, anxiety, or other mood changes.

Reviewer Comments: DRISK concurs with the proposed goals of the REMS.

9.2 REMS ELEMENTS

9.2.1 Prescriber Certification

Healthcare providers who prescribe SILIQ must be certified.

- a. To become certified to prescribe SILIQ, prescribers must:
 - i. Review the Prescribing Information (PI) for SILIQ.
 - ii. Enroll in the SILIQ REMS Program by completing the *SILIQ REMS Program Prescriber Enrollment Form*
- b. As a condition of certification, prescribers must:
 - i. Enroll each patient in the SILIQ REMS Program by performing the following:
 - 1) Prior to providing the first prescription, counsel the patient that suicidal ideation and behavior (SIB), including completed suicides, have occurred in patients treated with SILIQ by informing the patient of the following key safety information:
 - i. Suicidal ideation and behavior (SIB) events and symptoms may occur at any time during treatment with SILIQ.
 - ii. To be aware of symptoms of suicidal ideation and behavior (SIB) events and steps to take if SIB symptoms occur..
 - 2) Complete the *SILIQ REMS Program Patient-Prescriber Agreement Form* for each patient. Submit the completed form to the SILIQ REMS Program and store a copy in the patient's records.
 - 3) Provide the patient with the *SILIQ REMS Program Patient Wallet Card*
 - i. Understand that patients with new or worsening symptoms of depression or suicidality should be referred to a mental health professional, as appropriate.
 - ii. Inform SILIQ REMS Program if an enrolled patient has discontinued therapy or is no longer under your care.
- c. Valeant Pharmaceuticals North America LLC (Valeant) must:
 - i. Ensure that healthcare providers who prescribe SILIQ are certified, in accordance with the requirements described above.
 - ii. Provide all the following mechanisms for prescribers to complete the certification process for the SILIQ REMS Program: online, by email, and by fax.

- iii. Ensure that prescribers are notified when they have been certified by the SILIQ REMS Program.
- iv. Maintain a validated, secure database of prescribers who are certified to prescribe SILIQ in the SILIQ REMS Program.
- v. Ensure that prescribers meet the REMS requirements and de-certify prescribers who do not maintain compliance with REMS requirements.
- vi. Ensure that certified prescribers are provided access to the database of certified pharmacies and enrolled patients.
- vii. Provide the *SILIQ REMS Program Prescriber Enrollment Form*, *SILIQ REMS Program Patient-Prescriber Agreement Form*, *SILIQ REMS Program Patient Wallet Card*, and the Prescribing Information to healthcare providers who (1) attempt to prescribe SILIQ and are not yet certified, or (2) inquire about how to become certified.

Reviewer Comments: Prescriber certification is a necessary requirement of the REMS to ensure that the prescriber is informed of the risk of SIB. To become certified, a prescriber must review the Prescribing Information (PI) for SILIQ and complete an enrollment form (one time) to enroll in the REMS.

Prescribers must enroll each patient in the REMS program, provide them with counseling, and a SILIQ patient wallet card prior to prescribing SILIQ. The counseling and wallet card emphasize to patients the observed risk of suicidal ideation in subjects treated with SILIQ and the importance of seeking medical advice should signs of suicidal ideation or behavior, new onset or worsening depression, anxiety, or other mood changes emerge. Requiring prescribers to counsel the patient before prescribing brodalumab is intended to increase awareness about the serious risk of SIB. DRISK concurs with Valeant's proposed prescriber certification requirement.

SILIQ REMS Program Prescriber Enrollment Form

The form serves to inform the prescriber of the serious risk of SIB and that patients with new or worsening symptoms of depression or suicidality should be referred to a mental health professional, as appropriate. The form also educates the prescriber about their requirements under the REMS program, which include prescriber self-enrollment, enrollment of patients, patient counseling, and provision of a wallet card to each patient.

SILIQ REMS Program Patient-Prescriber Agreement Form

See Section 9.2.3 for additional details.

SILIQ REMS Program Website

The REMS program website will contain the Prescribing Information and all appended REMS program materials. All of these materials will be available in a format that can be downloaded from the website and printed; the materials may also be obtained by contacting the REMS Program Call Center.

SILIQ REMS Program Patient Wallet Card

See Section 9.2.3 for additional details.

Reviewer Comments: DRISK concurs with Valeant's proposed prescriber certification requirements and appended materials.

9.2.2 Pharmacy Certification

Pharmacies that dispense SILIQ must be certified.

- a. To become certified to dispense SILIQ, pharmacies must:
 - i. Designate an authorized representative to complete the enrollment process by submitting the completed *SILIQ REMS Program Pharmacy Enrollment Form* on behalf of the pharmacy.
 - ii. Ensure that the authorized representative oversees implementation and compliance with the SILIQ REMS Program requirements by the following:
 - 1) Review and complete the *SILIQ REMS Program Pharmacy Enrollment Form*.
 - 2) Ensure all relevant staff involved in the dispensing of SILIQ are informed of the SILIQ REMS Program requirements as described in the *SILIQ REMS Program Pharmacy Enrollment Form*.
 - 3) Put processes and procedures in place to ensure the following requirements are completed prior to dispensing SILIQ:
 1. Verify the prescriber is certified and the patient is enrolled in the SILIQ REMS Program by calling the SILIQ REMS Program or by accessing the SILIQ REMS Program Website.
- b. As a condition of certification, the certified pharmacies must:
 - i. Recertify in the SILIQ REMS Program if the pharmacy designates a new authorized representative.
 - ii. Dispense SILIQ to patients only after obtaining authorization by calling the SILIQ REMS Program or by accessing the SILIQ REMS Program Website. The authorization confirms the following:

- 1) The prescriber is certified in the SILIQ REMS Program; and
 - 2) The patient is enrolled in the SILIQ REMS Program
- iii. Maintain documentation that all processes and procedures are in place and are being followed for the SILIQ REMS Program and provide upon request to Valeant, FDA, or a third party acting on behalf of Valeant or FDA.
 - iv. Comply with audits by Valeant, FDA, or a third party acting on behalf of Valeant or FDA, to ensure that all processes and procedures are in place and are being followed for the SILIQ REMS Program.
- c. Valeant must:
- i. Ensure that pharmacies that dispense SILIQ are specially certified, in accordance with the requirements described above.
 - ii. Provide all the following mechanisms for pharmacies to complete certification for the SILIQ REMS Program: online, by email, and by fax.
 - iii. Ensure that pharmacies are notified when they have been certified by the SILIQ REMS Program.
 - iv. Ensure that certified pharmacies are provided access to the database of certified prescribers and enrolled patients.
 - v. Verify every year that the authorized representative's name and contact information correspond to those of the currently designated authorized representative for the certified pharmacy. If different, the pharmacy must be required to recertify with a new authorized representative.

Reviewer Comments: Brodalumab is expected to be used primarily in an outpatient setting, however, from a safety perspective, brodalumab could be dispensed by any certified outpatient or inpatient pharmacy because the product is typically self-administered at home. Pharmacies must be certified to receive drug from wholesaler/distributors, and must agree to the REMS requirements to dispense brodalumab. To obtain certification, pharmacies must enroll in the REMS by designating an authorized representative to complete the pharmacy enrollment form. The authorized representative will oversee their pharmacy's implementation of and compliance with the program requirements. Pharmacies will dispense SILIQ only after verifying that both the prescriber and patient are enrolled and authorized in the program; thereby ensuring that both the prescriber and patient are aware of the risk of SIB and that the patient has provided informed consent prior to receiving the first prescription for brodalumab.

DRISK concurs with Valeant's proposed pharmacy certification requirements.

SILIQ REMS Program Pharmacy Enrollment Form

The pharmacy enrollment form is completed by the pharmacy's authorized representative on behalf of the pharmacy. The form includes detailed language regarding the REMS requirements for pharmacies.

REMS Program Website

The REMS program website will contain all appended REMS program materials, which should be downloadable and printable for the duration of the REMS.

Reviewer Comments: DRISK concurs with the proposed pharmacy certification requirements and appended materials.

9.2.3 Documentation of Safe-Use Conditions (ETASU D)

SILIQ must be dispensed to patients with evidence or other documentation of safe-use conditions.

- a. To become enrolled in the SILIQ REMS Program, a patient must sign a *SILIQ REMS Program Patient-Prescriber Agreement Form* indicating that he/she has:
 - i. Received and has read the *SILIQ REMS Program Patient-Prescriber Agreement Form* with their healthcare provider.
 - ii. Received counseling from the prescriber regarding:
 - 1) the observed risk of suicidal ideation and behavior (SIB)
 - 2) the importance of keeping the *SILIQ REMS Program Patient Wallet Card* with them at all times
 - 3) the need to seek medical attention should they experience emergence or worsening of suicidal ideation and behavior
 - iii. Received the *SILIQ REMS Program Patient Wallet Card*
- b. Valeant must:
 - i. Provide all of the following mechanisms for the certified prescribers to be able to submit the completed *SILIQ REMS Program Patient-Prescriber Agreement Form* to the SILIQ REMS Program: online, by email, and by fax.

Reviewer Comments: Documentation of safe-use conditions is necessary to ensure that brodalumab is dispensed only to patients who have received counseling from the prescriber about the risks of SIB observed with brodalumab. Patients will be required to enroll in the REMS in order to receive the drug. To enroll in the REMS, a patient must sign a SILIQ REMS Program Patient-Prescriber Agreement Form. The form is intended to ensure that the patient has received counseling from the prescriber regarding: the risk of SIB, the importance of keeping the SILIQ REMS Program Patient Wallet Card with them at all times, and the need to seek medical attention should they experience emergence or worsening of suicidal ideation and behavior; the patient also attests that they have received the SILIQ REMS Program Patient Wallet Card.

The drug is dispensed only after the pharmacy confirms that both the prescriber and patient are certified and authorized in the REMS. The primary purpose of the safe-use conditions is to inform

patients of the observed risk of suicidal ideation in subjects treated with SILIQ and the importance of seeking medical advice should signs of suicidal ideation or behavior, new onset or worsening depression, anxiety, or other mood changes emerge. This safe use condition reflects similar activities that occurred after the protocol changes were implemented in the brodalumab clinical trials to address the risk of SIB. Requiring prescribers to counsel the patient before prescribing brodalumab may mitigate the serious risk of SIB and steps to take if they should occur.

SILIQ REMS Program Patient-Prescriber Agreement Form

Before starting brodalumab, each patient must be enrolled in the REMS program by a certified prescriber; the certified prescriber completes the patient-prescriber agreement form with the patient and submits the completed form to the SILIQ REMS Program

SILIQ REMS Program Patient Wallet Card

The certified prescriber agrees to provide the wallet card to each patient prior to the first prescription. As per the prescriber agreement, patients should be counseled to carry the wallet card at all times. The wallet card includes information about the risk of SIB and associated symptoms, as well as steps to take if any of these symptoms occur. The card includes contact information for the National Suicide Prevention Lifeline. The card may also be helpful in informing other prescribers and caregivers that the patient is taking SILIQ and the risk of SIB.

Reviewer Comments: DRISK concurs with the proposed documentation of safe-use conditions requirement and appended materials.

9.2.4 Implementation System

1. Valeant must ensure that SILIQ is only distributed to certified pharmacies by:
 - a. Ensuring that wholesalers/distributors who distribute SILIQ comply with the program requirements for wholesalers/distributors. The wholesalers/distributor must:
 - i. Put processes and procedures in place to verify, prior to distributing SILIQ, that the pharmacies are certified.
 - ii. Train all relevant staff on the SILIQ REMS Program requirements.
 - iii. Comply with audits by Valeant, FDA, or a third party acting on behalf of Valeant or FDA to ensure that all processes and procedures are in place and are being followed for the SILIQ REMS Program. In addition, wholesalers/distributors must maintain documentation to

support that all processes and procedures are in place, being followed, and make the documentation available for audits.

- iv. Provide distribution data to Valeant to verify compliance with the REMS.
 - b. Ensuring that wholesalers/distributors maintain distribution records of all shipments of SILIQ and provide the data to Valeant.
2. Valeant must monitor distribution data to ensure all the processes and procedures are in place and functioning to support the requirements of the SILIQ REMS Program.
3. Valeant must audit the wholesalers/ distributors within 90 calendar days after the wholesaler/distributor is authorized to ensure that all processes and procedures are in place and functioning to support the requirements of the SILIQ REMS Program.
4. Valeant must maintain a validated, secure database of prescribers and pharmacies that are certified to dispense SILIQ in the SILIQ REMS Program.
5. Valeant must maintain a validated, secure database of patients who are enrolled in the SILIQ REMS Program.
6. Valeant must maintain records of SILIQ certified prescribers, certified pharmacies, and enrolled patients to meet REMS requirements.
7. Valeant must maintain a SILIQ REMS Program Call Center (855-511-6135) and SILIQ REMS Program Website (www.SILIQREMS.com). The REMS Program Website must include the capability to confirm patient authorization status, and the option to print the Prescribing Information, Medication Guide, and SILIQ REMS materials. The SILIQ product website must include a prominent REMS-specific link to the SILIQ REMS Program Website. The SILIQ REMS Program Website must not link back to the product website(s).
8. Valeant must ensure that the SILIQ REMS Program Website is fully operational, including the capability to complete prescriber and pharmacy certification and patient enrollment online; online confirmation of patient authorization functionality; and the REMS materials listed in or appended to the SILIQ REMS document are available through the SILIQ REMS Program Website and by calling the SILIQ REMS Program Call Center.
9. Valeant must monitor on an ongoing basis the certified pharmacies to ensure the requirements of the SILIQ REMS Program are being met. Valeant must institute corrective action if noncompliance is identified and decertify pharmacies that do not maintain compliance with the REMS requirements.
10. Valeant must maintain an ongoing annual audit plan that involves certified pharmacies.
11. Valeant must audit 20% or one, whichever is greater, of the certified pharmacies 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 to support the requirements of the SILIQ REMS Program. The certified pharmacies must be identified in Valeant's ongoing annual audit plan. Valeant must institute corrective action if noncompliance is identified.

12. Valeant must take reasonable steps to improve implementation of and compliance with the requirements in the SILIQ REMS Program based on monitoring and evaluation of the SILIQ REMS Program.

Reviewer Comments: The implementation system supports distribution and dispensing requirements; the monitoring of compliance of distributors and certified entities with regard to dispensing and corrective actions; the institution of a secure database of patients and prescribers enrolled in the REMS; and the availability of a REMS program website and call center.

DRISK concurs with Valeant's proposed implementation system.

9.2.5 Timetable for Submission of Assessments

Valeant must submit REMS assessments to the FDA at 6 months and 12 months and annually thereafter from the date of the initial approval of the REMS. To facilitate inclusion of as much information as possible while allowing reasonable time to prepare the submission, the reporting interval covered by each assessment should conclude no earlier than 60 calendar days before the submission date for that assessment. Valeant must submit each assessment so that it will be received by the FDA on or before the due date.

9.3 REMS KEY RISK MESSAGES

SILIQ Risk Messages for Healthcare Providers

Risk Message #1: SILIQ can potentially cause suicidal ideation and behavior (SIB)

Prescribers must:

- Counsel patients about the observed risk of suicidal ideation and behavior observed with SILIQ therapy
- Inform patients to seek medical attention should they experience emergence or worsening of suicidal thoughts and behavior
- Enroll him/herself in the SILIQ REMS Program
- Enroll each patient in the SILIQ REMS Program
- Complete the *SILIQ REMS Program Patient-Prescriber Agreement Form* for each patient by submitting the completed form to the SILIQ REMS Program and store a copy in the patient's records

- Provide each patient with the *SILIQ REMS Program Patient Wallet Card*
-

Reviewer Comments: DRISK concurs with Valeant’s proposed Key Risk Messages for Healthcare Providers.

SILIQ Risk Messages for Pharmacists

Risk Message #1: Pharmacies must be certified in order to dispense SILIQ.

Pharmacies must:

- Designate an authorized representative to complete the enrollment process and submit the completed SILIQ REMS Program Pharmacy Enrollment Form on behalf of the pharmacy

Reviewer Comments: DRISK concurs with Valeant’s proposed Key Risk Messages for Pharmacists. This reviewer would prefer to also include that, before dispensing each SILIQ prescription, pharmacies must ensure that the prescriber is certified and the patient is enrolled.

SILIQ Risk Messages for Patients

Risk Message #1: Patients should be aware of the observed risk of suicidal ideation and behavior (SIB).

Risk Message #2: Patients should receive and carry the *SILIQ REMS Program Patient Wallet Card* with them at all times.

Risk Message #3: Patients should seek medical attention should they experience emergence or worsening of suicidal ideation and behavior (SIB).

Reviewer Comments: DRISK concurs with Valeant’s proposed Key Risk Messages for Patients.

9.4 REMS ASSESSMENT PLAN

The REMS Assessment Plan submitted by the Applicant on February 13, 2017 is as follows:

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, race, gender)
 - 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, race, gender)
- 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 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 of SILIQ REMS requirements and processes.

6. The requirements for assessments of an approved REMS under section 505-1(g)(3) include with respect to each goal included in the strategy, an assessment of the extent to which the approved strategy, including each element of the strategy, is meeting the goal or whether 1 or more such goals or such elements should be modified .

Reviewer Comments: DRISK concurs with Valeant's proposed REMS Assessment Plan.

10 Discussion of Need for a REMS

Moderate to severe psoriasis is a serious and, at times, disabling condition that has a substantial impact on patients' lives. The benefits of treatment with brodalumab were demonstrated by meeting the co-primary endpoints of the clinical trials. Based on these results, brodalumab was found to be highly efficacious for the treatment of adult patients with moderate to severe plaque psoriasis who are candidates for systemic therapy or phototherapy and have failed to respond or have lost response to other systemic therapies.

SIB events in the brodalumab clinical trials occurred at any time during treatment and resulted in serious outcomes. There were 6 completed suicides (4 in the psoriasis program) during the brodalumab clinical trials, which subsequently led to the early discontinuation of all brodalumab trials across all indications. DDDP consulted other divisions within CDER in order to gain a greater understanding of the potential risk of suicidal ideation and behavior associated with brodalumab use. The DEPI-I reviewers concluded that there was an inordinate number of completed suicides in the brodalumab trials, compared to other psoriasis biologics. The DPV reviewer recommended that brodalumab be reserved as a second-line treatment as well as consideration of risk mitigation strategies to address the potential risk of SIB.^p Further, the DB-7 subgroup analysis of SIB incidence rate by history of suicidality resulted in a 12- to 18-fold increase among subjects with history, compared to those without.^q

This risk was discussed during an AC meeting, from which we received the following comments: Brodalumab is efficacious and would meet a strong need; however, SIB is a serious

^p Chiang G., Division of Dermatology and Dental Products. Clinical Review for Brodalumab, BLA 761032, August 25, 2016.

^q Lan L. Division of Biostatistics-VII, Consultative Review of Brodalumab, dated July 6, 2016.

concern that patients and prescribers need to be made aware of; six completed suicides cannot be ignored; risk management measures beyond labeling are needed. The results of the voting and discussion from the AC meeting were subsequently presented to the ROC, in addition to possible risk management strategies to address the potential risk of SIB. The ROC determined that a REMS with ETASU was necessary to ensure the benefits of brodalumab outweigh its risks of SIB.

Two separate meetings of the REMS Oversight Committee (ROC) were held to discuss various options to address the risk of SIB observed with brodalumab, including labeling and no REMS, a Communication Plan-only REMS, and a REMS with ETASU. The ROC concluded that a REMS with ETASU is necessary to mitigate the risk of suicidality. After considering recommendations from the ROC and the Dermatologic and Ophthalmic Drugs Advisory Committee, DRISK and DDDP determined a REMS with ETASU is necessary to ensure the safe use of the drug.

The Agency determined that the REMS should be designed to ensure that the prescriber and patient are informed of the risk of SIB observed in the brodalumab clinical program prior to starting treatment and to emphasize that patients need to seek medical help if they experience SIB. To achieve this, the minimum necessary elements of the REMS are: prescriber certification (ETASU A), pharmacy certification (ETASU B), and documentation of safe-use conditions (i.e., patient enrollment) (ETASU D).

11 Conclusion and Recommendations

The totality of the SIB risk associated with brodalumab is serious, and it is necessary to ensure that prescribers are informed of these risks the importance of informing patients about the risk before they start treatment, and the need to counsel patients about SIB symptoms and the steps to take if they occur. Based on the magnitude and severity of the risk of SIB, a REMS consisting of elements to assure safe use to include prescriber certification (A), pharmacy certification (B), and documentation of safe-use conditions (D) is necessary to ensure that the benefits outweigh the risks. A REMS will ensure that both the prescriber and the patient are informed about the risk of SIB prior to the patient's first prescription. The REMS will be used to communicate that patients with new or worsening symptoms of depression or suicidality should be referred to a mental health professional, as appropriate, and patients should be counseled to seek medical help if they experience symptoms associated with SIB.

On February 13, 2017, Valeant submitted an amended REMS proposal that consists of ETASU that include prescriber certification, pharmacy certification, and documentation of safe-use conditions; an implementation system; and a timetable for submission of assessments. DRISK finds the submission acceptable; therefore, DRISK recommends approval of the REMS submitted on February 13, 2017.

12 Materials Reviewed

The following is a list of materials informing this review:

1. AstraZeneca, Clinical Overview for Brodalumab, BLA 761032, November 16, 2015.
2. AstraZeneca, Summary of Clinical Safety for Brodalumab, BLA 761032, November 16, 2015.
3. 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).
 - o Amendment received January 17, 2017 (Seq. 0065).
 - o Amendment received February 10, 2017 (Seq. 0071).
 - o Amendment received February 13, 2017 (Seq. 0073).
4. AstraZeneca, 4-month Safety Update for Brodalumab, BLA 761032, March 15, 2016.
5. AstraZeneca, Proposed Prescribing Information for Brodalumab, November 16, 2015.
6. Mosholder A. and Anic G. DEPI-I. Consultative Review of Brodalumab Clinical Trial Data, BLA 761032, March 22, 2016.
7. Division of Dermatology and Dental Products, Mid-Cycle Meeting Clinical Slides, Brodalumab, BLA 761032, April 20, 2016.
8. Kim J. DPP. Consultative Review for BLA 761032 (Brodalumab), April 25, 2016.
9. REMS Oversight Committee (ROC) Presentation, May 25, 2016.
10. Senatore F. Division of Cardiovascular and Renal Products (DCRP), Consultative Review for Brodalumab (BLA 761032), June 30, 2016.
11. Lan L. Division of Biostatistics-VII, Consultative Review of Brodalumab (BLA 761032), July 6, 2016.
12. Dermatologic and Ophthalmic Drugs Advisory Committee Presentation, July 19, 2016.
13. ROC Presentation, August 9, 2016.
14. Chiang G. DDDP. Clinical Review for Brodalumab (BLA 761032), August 25, 2016.
15. Applicant's website, www.Valeant.com, accessed September 22, 2016.
16. Valeant, REMS Correspondence to BLA 761032, received October 4, 2016 (Seq. 0055).
17. Medina R. Division of Medical Policy Programs (DMPP), Patient Labeling Review for Brodalumab (BLA 761032), November 16, 2016.
18. South E. DRISK, Review of REMS Proposal for BLA 761032 (Brodalumab), December 12, 2016.
19. Valeant, REMS Correspondence to BLA 761032, received December 16, 2016 (Seq. 0062).
20. Valeant, REMS Correspondence to BLA 761032, received December 22, 2016 (Seq. 0063).
21. Valeant, REMS Correspondence to BLA 761032, received December 23, 2016 (Seq. 0064).

22. Fitzgerald D. and South E. DRISK, Review of REMS Proposal for BLA 761032 (Brodalumab), January 9, 2017.
23. Valeant, REMS Correspondence/Amendment to BLA 761032, received January 17, 2017 (Seq. 0065).
24. Valeant, REMS Correspondence to BLA 761032, received January 23, 2017 (Seq. 0067).
25. Valeant, REMS Correspondence to BLA 761032, received February 3, 2017 (Seq. 0069).
26. Dixon S. DDDP, Draft minutes of January 23, 2017 teleconference between Agency and Valeant, viewed February 6, 2017.

13 Appendices

47 Page(s) has been Withheld in Full as duplicate of REMS immediately following this page

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/s/

ERIN M SOUTH
02/15/2017

JAMIE C WILKINS PARKER
02/15/2017

CYNTHIA L LACIVITA
02/15/2017
Concur

Risk Evaluation and Mitigation Strategy (REMS) Memorandum

U.S. FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
OFFICE of DRUG EVALUATION III
DIVISION of DERMATOLOGY and DENTAL PRODUCTS

BLA #s: 761032
Products: Siliq (brodalumab) Injection, 210 mg/1.5 mL
APPLICANT: Valeant Pharmaceuticals Luxembourg S.a.r.l. (VPL)
FROM: Tatiana Oussova, MD, MPH, Deputy Director for Safety
DATE: February 14, 2017

Section 505-1 of the Federal Food, Drug, and Cosmetic Act (FDCA) authorizes FDA to require the submission of a risk evaluation and mitigation strategy (REMS) if FDA determines that such a strategy is necessary to ensure that the benefits of the drug outweigh the risks [section 505-1(a)]. Section 505-1(a)(1) provides the following factors:

- (A) The estimated size of the population likely to use the drug involved;
- (B) The seriousness of the disease or condition that is to be treated with the drug;
- (C) The expected benefit of the drug with respect to such disease or condition;
- (D) The expected or actual duration of treatment with the drug;
- (E) The seriousness of any known or potential adverse events that may be related to the drug and the background incidence of such events in the population likely to use the drug;
- (F) Whether the drug is a new molecular entity (NME).

After consultations between the Office of New Drugs and the Office of Surveillance and Epidemiology, we have determined that a REMS that includes elements to assure safe use is necessary for Siliq (brodalumab) Injection, 210 mg/1.5 mL to ensure that the benefits of the drug outweigh the risk of observed suicidal ideation and behavior (SIB) in subjects treated with Siliq. In reaching this determination, we considered the following:

A. Psoriasis is a chronic immune-mediated inflammatory disease affecting 2-3% of the U.S. population. Plaque psoriasis is the most common form, accounting for 85-90% of cases. Approximately 20% of patients have moderate to severe disease affecting more than 5% of their body surface area.

B. Psoriasis is a common, chronic, inflammatory, multi-system disease with predominantly skin and joint manifestations. It can present in many different patterns from the scalp to the feet and cause psychiatric distress and physical disabilities. Moderate-to-severe psoriasis is a serious and, at times, disabling condition that has a substantial impact on patients' lives. Psoriasis is associated with other serious comorbidities, including autoimmune disease, cardiovascular disease, and metabolic syndrome.

C. There are multiple drugs approved for psoriasis that have an acceptable risk-benefit profile and achieve moderate-to-high efficacy for the treatment of moderate-to-severe disease. All of the products have one or more serious risks. Because of the potential for lack of response, loss of response, comorbidities, concomitant illnesses, as well as other individual factors that may impact clinical decision-making, there is a need for additional therapeutic options. The benefits of treatment with brodalumab were demonstrated by meeting the co-primary endpoints of the clinical trials. Based on these results, brodalumab was found to be highly efficacious for the treatment of adult patients with moderate-to-severe plaque psoriasis who are candidates for systemic therapy or phototherapy.

D. Based on brodalumab safety profile, specifically the risk of SIB, it will be indicated for patients who have failed to respond or have lost response to other systemic therapies for the treatment of moderate-to-severe plaque psoriasis. For this reason, we anticipate that the likely prescribers of brodalumab will be dermatologists. The dispensing of brodalumab, which will be packaged as a single-dose prefilled syringe for subcutaneous injection (b) (4), could be performed by any outpatient or inpatient pharmacy, and it is expected that this product would be self-administered by patients or administered to patients by caregivers in the home setting. It is difficult to predict how frequently patients will follow-up with the prescriber. If patients are tolerating and responding well to treatment, the frequency of their follow-up office visits may be expected to be reduced. The frequency of administration is every 2 weeks.

Prescribers will have an important role in managing the risk of suicidal ideation and behavior with brodalumab. Dermatologists have experience with other systemic therapies for psoriasis, including other IL-17-targeted therapies as well as other biologics that have severe toxicities and serious adverse events. It is important that both prescribers and patients are aware of the potential risk. Prescribers should thoughtfully consider this when determining appropriate patient selection. Ensuring that prescribers and patients are informed about the potential risk of SIB observed with brodalumab is necessary to mitigate the risk.

E. Patients with psoriasis face numerous social and psychological challenges. In a study conducted in the U.K.'s General Practice Research Database, the incidence of clinical depression and suicidality in patients with psoriasis was higher than in the general population. Among patients with psoriasis, the incidence of clinical depression and suicidality was higher for those on systemic therapy than for those who were not (i.e., for patients presumed to have severe vs. mild disease).

1. For the purpose of clinical review, suicidal ideation and behavior (SIB) is defined as a completed suicide, a suicide attempt, or a suicide behavior and suicide ideation.
2. Cumulatively, through September 30, 2015 (termination of the clinical studies for brodalumab for safety reason), there were a total of 39 SIB events in 34 subjects, with 6 completed suicides (4 in the psoriasis program, one in the rheumatoid arthritis program, and one in the psoriatic arthritis program). There were 12 suicide attempts in 8 subjects; 6 suicidal behaviors in 6 subjects; and 20 suicidal ideations in 18 subjects; which led to the early discontinuation of all brodalumab trials **across all indications**.

3. In the psoriasis development program, 35 SIB events occurred in 4464 brodalumab users, resulting in an incidence of 0.78% (95% CI: 0.63–1.25) and the follow-up time-adjusted incidence rate was 0.38 per 100 subject-years (95% CI: 0.27–0.53). Notably, the subgroup analysis of SIB incidence rate by history of suicidality resulted in a 12- to 18-fold increase among subjects with history compared to those without.
4. We compared the data on SIB in the brodalumab trials to data on SIB events observed in clinical development programs for other psoriasis biologics. Based on available data, the calculated rate of suicide in patients taking brodalumab (all indications) is 58 per 100,000 patient-years (PY), which is 3-4 times higher than the rate of suicide in clinical trials of other biologics. In the United States in 2013, the reported rate of completed suicides was 12.6 per 100,000 patient-years, and approximately 9.3 million adults (3.9% of the adult U.S. population) reported having suicidal thoughts in the past year.
5. The brodalumab safety concerns were presented to the FDA Dermatologic and Ophthalmic Drugs Advisory Committee (AC) on July 19, 2016. The majority of the committee agreed that clinicians and patients need to be made aware of the possibility of the risk of SIB. The AC unanimously agreed that brodalumab should be approved. Fourteen committee members voted for the addition of risk management options beyond labeling to mitigate SIB; of those 14, the majority supported a registry of some type.
6. Other important adverse events (AEs) associated with the use of brodalumab appear to be serious infections, tuberculosis, and Crohn's disease. Brodalumab is contraindicated in patients with Crohn's disease.

F. Siliq is a new molecular entity.

The elements of the REMS will be elements to assure safe use, including that healthcare providers who prescribe Siliq must be specially certified, pharmacies that dispense Siliq must be specially certified, and that Siliq must be dispensed only to patients with evidence or other documentation of safe-use conditions; implementation system, and a timetable for submission of assessments of the REMS.

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/s/

TATIANA OUSSOVA
02/14/2017