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RESEARCH**

*APPLICATION NUMBER:*

**761032Orig1s000**

**OFFICE DIRECTOR MEMO**

<b>Date</b>	February 8, 2017
<b>From</b>	Julie Beitz, MD
<b>Subject</b>	Office Director Memorandum
<b>NDA/BLA #</b>	BLA 761032
<b>Applicant Name</b>	Valeant Pharmaceuticals Luxembourg S.a.r.l. (VPL)
<b>Date of Submission</b>	November 16, 2015
<b>PDUFA Goal Date</b>	February 16, 2017 (Review clock extended due to receipt of a major amendment on October 18, 2016)
<b>Proprietary Name / Established (USAN) Name</b>	Siliq/ brodalumab
<b>Dosage Forms / Strength</b>	Single-dose prefilled syringe for injection/210 mg of brodalumab in 1.5 mL solution (140 mg/mL)
<b>Action:</b>	Approval
<b>Approved Indication(s)/Populations</b>	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

### Regulatory Action

I concur with the recommendations of Kendall Marcus, MD, Director, Division of Dermatology and Dental Products, and Amy Egan, MD, Deputy Director, Office of Drug Evaluation III, to approve Siliq (brodalumab) 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.

Dr. Egan's archived memorandum, dated December 28, 2016, is a comprehensive summary of the key safety and efficacy findings presented in BLA 761032, and delineates her assessment of the drug's benefits and risks. In the interim, discussions regarding product labeling and the elements of the Siliq Risk Evaluation and Mitigation Strategy (REMS) have concluded and the application is now ready for approval.

The risk of suicidal ideation and behavior reported with the use of Siliq in clinical trials will be described in a **Boxed Warning**. The **Indications and Usage** section will state that Siliq is intended 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. The **Dosage and Administration** section will state that if an adequate response has not been achieved after 12 to 16 weeks of treatment consideration should be given to discontinuing therapy with Siliq.

To ensure that the benefits of treatment outweigh the serious risk of suicidal ideation and behavior, Siliq will only be available under a REMS with elements to ensure safe use (ETASU). Notable requirements of the Siliq REMS include the following:

- Prescribers must be certified with the program and counsel patients about the risks of suicidal ideation and behavior. Patients with new or worsening symptoms of depression or suicidality should be referred to a mental health professional, as appropriate.
- Patients must sign a Patient-Prescriber Agreement Form and be made aware of the need to seek medical attention should they experience new or worsening suicidal thoughts or behavior, feelings of depression, anxiety or other mood changes.
- Pharmacies must be certified with the program and must only dispense to patients who are authorized to receive Siliq.

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/s/  
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JULIE G BEITZ  
02/08/2017

Office Deputy Director Decisional Memo

<b>Date</b>	December 28, 2016
<b>From</b>	Amy G. Egan, MD, MPH
<b>Subject</b>	Office Deputy Director Decisional Memo
<b>NDA/BLA #</b>	BLA 761032
<b>Applicant Name</b>	Valeant Pharmaceuticals Luxembourg S.a.r.l. (VPL)
<b>Date of Submission</b>	November 16, 2015
<b>PDUFA Goal Date</b>	November 16, 2016 (extended to February 16, 2017 due to a major amendment received October 18, 2016)
<b>Proprietary Name / Established (USAN) Name</b>	Siliq/ brodalumab
<b>Dosage Forms / Strength</b>	Single-dose prefilled syringe for injection/210 mg of brodalumab in 1.5 mL solution (140 mg/mL)
<b>Applicant Proposed Indication(s)</b>	For the treatment of moderate to severe plaque psoriasis in adult patients who are candidates for systemic therapy or phototherapy.
<b>Action:</b>	Approval, pending finalization of the labeling and REMS.
<b>Approved Indication(s)/Populations</b>	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>Material Reviewed/Consulted</b>	<b>Names of discipline reviewers</b>
Medical Officer Review	Gary Chiang, MD, MPH
CDTL Review	David Kettl, MD
Division Director Review	Kendall Marcus, MD (pending at the time of this review)
Statistical Review	Carin Kim, PhD
Pharmacology Toxicology Review	Carmen Booker, PhD
OPQ Review	Qing Zhou, PhD
Microbiology Review	Maria Jose Lopez-Barragan, PhD
Clinical Pharmacology Review	Jie Wang, PhD
Pharmacometrics Reviewer	Dhananjay Marathe, PhD
DPP	Jean Kim, MD, MA
DEPI I	Andrew D. Mosholder, MD, MPH; Gabriella Anic, PhD, MPH
DPMH	Christos Mastroyannis, MD (maternal health)
COA	Yasmin Choudhry, MD
OPDP	Silvia Wanis, PharmD
DMPP	Rowell Medina, PharmD, BCPS
DB VII	Ling Lan, Ph.D.
OSI	Roy Blay, PhD
OSE/DMEPA	Carlos Mena-Grillasca, RPh
OSE/DRISK	Erin Hachey, Pharm.D.
OSE/DPV	Jessica Weintraub, PharmD, BCPS

CDTL=Cross-Discipline Team Leader  
 OPQ=Office of Pharmaceutical Quality  
 DPP=Division of Psychiatry Products  
 DEPI I=Division of Epidemiology I  
 DPMH=Division of Pediatric and Maternal Health  
 COA=Clinical Outcome Assessment  
 OPDP=Office of Prescription Drug Promotion  
 DMPP=Division of Medical Policy  
 DB VII=Division of Biometrics VII  
 OSI=Office of Scientific Investigations  
 OSE= Office of Surveillance and Epidemiology  
 DMEPA=Division of Medication Error Prevention and Analysis  
 DRISK=Division of Risk Management  
 DPV=Division of Pharmacovigilance

#### Benefit-Risk Summary and Assessment

Siliq (brodalumab) is a subcutaneously administered human interleukin-17 receptor A antagonist. This memo documents my rationale for my Approval recommendation for BLA 761032 for Siliq (brodalumab) injection 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 efficacy of Siliq was established in three pivotal phase 3 trials. Relative to placebo, Siliq 210 mg every 2 weeks demonstrated superiority on the co-primary endpoints of proportion of subjects with sPGA of 0 or 1 at Week 12 and proportion of subjects with PASI 75 at Week 12, as well as the key secondary endpoints of PASI 100, and sPGA of 0 at Week 12. Across the phase 3 trials, response rates for PASI 75 ranged from 83% to 86% in patients treated with Siliq, versus 3% to 8% in the placebo group; response rates for sPGA of 0 or 1 ranged from 76% to 80% in patients treated with Siliq, versus 1% to 4% in the placebo group. The maximal effect of Siliq on sPGA of 0 or 1 was achieved by week 12, with some gain in responders with treatment from week 12 to week 16, but limited probability of becoming a responder beyond week 16. The efficacy of Siliq (brodalumab) is not in dispute. Siliq is a highly efficacious treatment, but when viewed in the context of already approved psoriasis therapies, the additional benefits appear nominal. In cross-trial comparisons, Siliq's efficacy on PASI 75 and sPGA 0 or 1 is comparable to that of infliximab and ixekizumab, and efficacy on PASI 100 is similar between Siliq and ixekizumab. Its subcutaneous route of administration is preferable to the intravenous administration required for infliximab, but is shared by all of the other approved biologics for psoriasis. Its maintenance dosing regimen places it among the least favorable of the approved biologics: ustekinumab requires dosing every 12 weeks; infliximab every 8 weeks; secukinumab and ixekizumab every 4 weeks; while Siliq and adalimumab require dosing every 2 weeks. An important benefit of Siliq may be its efficacy in patients who have failed prior biologic therapies. In post-hoc analyses of PASI-75 response in patients who had failed previous biologic psoriasis therapies, 82% of Siliq-treated patients achieved success across the three phase 3 trials, and PASI-90 and PASI-100 response rates were 65% and 35%, respectively. These patients, with more limited treatment options, may be willing to tolerate a greater level of risk to achieve benefit.

While Siliq shares safety concerns with other approved biologic psoriasis therapies (Crohn's disease exacerbation, infections, TB reactivation, response to live vaccines), the serious risk unique to Siliq is completed suicide. Four completed suicides (0.09%) occurred in subjects treated with SILIQ in the psoriasis program, compared with none in placebo subjects; across all

clinical development programs for Siliq, there were 6 completed suicides. The applicant has argued that the completed suicides represent the background risk in the psoriasis population, and that their development program, unlike others in the class, allowed enrollment of patients with pre-existing psychiatric disorders. However, while numerous studies in the literature have acknowledged an increased risk of suicidal ideation and behavior (SIB) among patients with psoriasis, an increased risk of completed suicide has not been demonstrated<sup>1</sup>. Further, while the exclusion criteria in the Siliq development program were more liberal, the percent of Siliq-treated patients in the psoriasis development program with baseline history of depression was low (10%), relative to the high background rate in the psoriasis population (estimated prevalence of about 44% [range: 28% to 67%]), and was similar to the percent of ixekizumab-treated and secukinumab-treated patients in their psoriasis development programs (9% and 8%, respectively). While causality cannot be unequivocally established, and while a precise biologic mechanism cannot be identified, the occurrence of six completed suicides in patients receiving Siliq in clinical development programs cannot be ignored.

Based on this potential safety signal, as well as the availability of alternative treatments with similar efficacy profiles, several disciplines have opined that Siliq should not be approved. I have considered these opinions, as well as other considerations, including the seriousness of the disease, the chronic nature of the disease, the variability in response and duration of response to different treatments, patient's ability to access various approved treatments, the impact of the disease on patients and their families, and the continued unmet medical need. Perhaps most importantly, I have considered the importance of patient autonomy. I believe that patients should have choice, but that choice must be informed. As articulated by Dr. Elaine Morrato at the July 19<sup>th</sup> Dermatologic and Ophthalmic Drugs Advisory Committee (DODAC): "For me, overall, it is very important that the whole communication is to ensure that there is informed consent and discussion between the prescriber and the patient so that no one down the road, a family member says if only I had known." The mechanism to ensure that a patient is fully informed has traditionally rested on the provision of a Medication Guide. However, this passive measure only ensures that the patient receives a document outlining the major risks of a product; it does not ensure that the patient will read or understand the content. The applicant had proposed a Risk Evaluation and Mitigation Strategy (REMS) with a Communication Plan; however, reliance on product labeling and a Dear Healthcare Provider letter to ensure that a

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<sup>1</sup> Egeberg A et al. Risk of self-harm and non-fatal suicide attempts, and completed suicide in patients with psoriasis – a population-based cohort study. *Br J Dermatol.* 2016;175(3):493-500

healthcare provider will provide the information necessary to ensure a patient's "informed consent" has proven largely unsuccessful<sup>2</sup>. The DODAC was clear that providers and patients must be made aware of the suicidality signal, but they were also clear that access to the drug should not be overly burdensome. Much of the DODAC's discussion focused on the need for a voluntary versus a mandatory registry, to obtain an estimate of the risk of suicidal behavior with Siliq. The only mechanism that the Agency has for requiring a mandatory registry is through a REMS with ETASU. The Agency considered a mandatory patient registry, but considered it overly burdensome, especially in light of the fact that it would be unlikely to answer the question of whether Siliq is causally related to suicidal behavior. The Agency sought a middle ground that would make the product available to patients who would receive the greatest benefit from the drug, while ensuring that prescribers would counsel their patients on the potential suicidal risk associated with the product, and that patients would acknowledge receiving such counseling and understanding of the risk.

This resulted in the following labeling and REMS requirements:

- A Boxed Warning on the serious risk of suicidal ideation and behavior.
- An indication that limits use of Siliq to patients who have failed to respond, or lost response, to other systemic therapies.
- A recommendation to reassess the need to continue therapy in patients who do not achieve an adequate response after 12-16 weeks.
- A REMS with ETASU that includes a one-time prescriber certification, a one-time pharmacy certification, and documentation of safe use conditions. This will (1) ensure that prescribers are informed of the serious risk of suicidal behavior observed with Siliq, acknowledge understanding of the risk, and agree to counsel patients about the risk; (2) require pharmacies to ensure that Siliq prescribers are certified and patients are enrolled in the Siliq REMS Program; and (3) ensure that patients are counseled by their prescribers on the serious risk of suicidal behavior, understand the risk, and are aware of the need to seek medical attention should they experience an emergence or worsening of suicidal thoughts or behavior. In conjunction with the counseling, prescribers will provide patients with a wallet card that contains information regarding warning signs of suicide and the telephone number of the National Suicide Prevention Lifeline.

There are those who will find our decision to approve the drug reckless and unsafe, while others will find the restrictions on

<sup>2</sup> FDA Risk Communication Advisory Committee, December 17, 2013; FDA Health Professional Organization Meeting, October 2012; Aggregate REMS Assessment information submitted by sponsor

the approval overly burdensome and paternalistic. However, I believe that the measures being put into place will make a highly efficacious drug available to patients in whom the benefit is greatest, and the risk acceptable. People will argue that there will be a delay in accessing the drug; however, data show that such delays already exist in the market place. Between 2009 and 2014, insurance coverage of biologics for moderate-to-severe plaque psoriasis has become more tightly regulated by insurance companies. In a recent study, the proportion of patients who required prior authorization (PA) forms to obtain biologics increased from 16% in 2009 to 75% in 2014. Additionally, the mean time between PA submission and receiving a response from the insurance company increased over the 5-year time period from 3.7 days to 6.7 days, and the rate of denials increased from 0% to 19%, with the most common reason for denial being failure to try alternate therapies prior to receiving biologics<sup>3</sup>. Therefore, I believe it is unlikely that the proposed labeling and REMS with ETASU will pose added restrictions or cause further delays. There will be those who argue that there are other drugs with suicidality signals, for which FDA has not required a REMS with ETASU. However, the presence of a rare, fatal event observed in a controlled clinical trial setting is merely the ‘tip of the iceberg’. Once approved and used in a broader population, we can anticipate a higher occurrence. Further, I am unaware of any product having been approved by the FDA with four completed suicides in a clinical development program.

We have also considered ways to further assess the suicidality signal in the post-marketing setting. Enhanced pharmacovigilance will improve the quality of reporting of suicidal behaviors, but because reporting is voluntary, it will not be able to provide a true estimate of the risk. ARIA is not currently equipped to reliably identify suicides and suicide attempts in its databases. The applicant has proposed use of the existing CORRONA psoriasis registry; however, the registry is voluntary and follow-up is too infrequent to allow for adequate monitoring of this rare event. There are those who have recommended a randomized, controlled trial (RCT) comparing Siliq to another biologic psoriasis therapy that does not have a suicide risk; however, given the rarity of the event (suicide attempts + completed suicides), sample size requirements, duration of follow-up required, the suitability of potential comparators, and other ethical considerations, such a trial is simply infeasible. Finally, a prospective observational study has been recommended that would rule out the presence of an unacceptable risk, e.g., ≥2-fold risk relative to other approved biologic psoriasis treatments. This may provide some estimate of the risk; however, because Siliq is being approved with a Boxed Warning and second-line indication, the estimate may be unreliable since patients with lower suicide risk would be more likely to be prescribed Siliq. An RCT which monitors PHQ-8, eCSSRS, and impulse control measures, e.g., the Barratt Impulsivity Scale and/or the Impulsiveness Scale from the Eysenck Personality

<sup>3</sup> Abdelnabi M et al. Insurance Coverage of Biologics for Moderate-to-Severe Psoriasis: A Retrospective, Observational 5-Year Chart Review. *Am J Clin Dermatol*. 2016;17:421-424.

Questionnaire, along with other potential biomarkers (IL-6, kynurenines, TNF- $\alpha$ ), may be helpful in determining which patients are at higher risk of SIB, or in identifying instruments that may predict risk. However, a negative study is unlikely to inform labeling, and the instruments themselves are not 'fit for purpose' for use in the clinical setting, especially by practicing dermatologists. Because of these limitations in our ability to reliably assess this signal in the post-market setting, I do not believe that FDA should require a study or trial that is doomed from the outset. That simply does not serve the public interest. Labeling and the REMS will convey our current understanding of this safety signal to providers and patients.

There are no inspectional issues that preclude approval. PMRs and PMCs have been agreed to. This application is approvable, pending finalization of the labeling and REMS. An addendum to this review will be provided when these have been satisfactorily concluded.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
<a href="#">Analysis of Condition</a>	<p>Psoriasis is a chronic immune-mediated inflammatory disease affecting 2-3% of the U.S. population. Skin and joint manifestations predominate. Plaque psoriasis is the most common form, accounting for 85-90% of cases. Skin lesions are circumscribed, scaly and erythematous and often symmetrically distributed over the body. Affected skin may be painful, cracked or itchy. The majority of cases of psoriasis are mild to moderate, but 20% have moderate to severe disease, affecting more than 5% of body surface area.</p> <p>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</p>	<p>Psoriasis is a relatively common, chronic immune-mediated inflammatory disease. Skin and joint manifestations predominate. Approximately 20% of patients have moderate to severe disease affecting more than 5% of their body surface area.</p> <p>Patients with psoriasis face numerous social and psychological challenges. The incidence of clinical depression and suicidality is higher among patients with psoriasis than in the general population.</p>

	<p>disease).<sup>4</sup></p> <p>Psoriasis is associated with other serious comorbidities, including autoimmune disease, cardiovascular disease, and metabolic syndrome.</p>	
<p><u>Current Treatment Options</u></p>	<p>Although numerous topical therapies are FDA-approved for plaque psoriasis, adult patients with moderate-to-severe plaque psoriasis have skin involvement that covers too large a surface area for these therapies to be practical or acceptable. Therefore, systemic therapies are typically indicated.</p> <p>Currently approved systemic therapies indicated for moderate-to-severe plaque psoriasis include the tumor necrosis factor inhibitors (adalimumab and etanercept), apremilast (a phosphodiesterase 4 inhibitor), ustekinumab (an antagonist of IL-12 and IL-23), secukinumab and ixekizumab (antagonists of IL-17A). The following systemic therapies are indicated for severe plaque psoriasis: methotrexate (an antimetabolite), the tumor necrosis factor inhibitor infliximab, cyclosporine (a T cell inhibitor), acitretin (a retinoid), and phototherapy.</p> <p>Based on cross-study comparison of PASI 75 response rates for the systemic agents, PASI 75 was achieved in &gt;70% of patients (highly efficacious) for cyclosporine, infliximab, adalimumab, ustekinumab, secukinumab, and ixekizumab; PASI 75 was achieved in &gt; 40% of patients (moderately</p>	<p>There are a number of FDA-approved therapies for adult patients with moderate to severe plaque psoriasis who are candidates for systemic therapy. Efficacy of these products ranges from highly efficacious to somewhat efficacious, but none provide permanent cure or universal response. 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 need for additional therapeutic options.</p>

<sup>4</sup> Olivier C, Robert P. D., Daihung D., Urba G., Catalin P., Hywel W., Kurd S. K., Troxel A. B., Crits-Christoph P., Gelfand J. M. The risk of depression, anxiety, and suicidality in patients with psoriasis: A population-based cohort study. Arch Dermatol 2010; 146(8): 891-895.

	<p>efficacious) for methotrexate and etanercept; and PASI 75 was achieved in &gt; 20% of patients (somewhat efficacious) for acitretin and apremilast. Phototherapy has been found to be highly efficacious as well.</p> <p>Safety concerns associated with approved therapies include:</p> <ul style="list-style-type: none"> <li>• Hepatotoxicity (methotrexate)</li> <li>• Nephrotoxicity (cyclosporine, methotrexate)</li> <li>• Risk of serious infections (tumor necrosis factor inhibitors, ustekinumab, secukinumab, ixekizumab, and cyclosporine)</li> <li>• Risk of malignancy/lymphoma (methotrexate, tumor necrosis factor inhibitors, ustekinumab, and cyclosporine)</li> <li>• Teratogenicity (acitretin, methotrexate)</li> <li>• Depression (apremilast)</li> <li>• Skin aging/skin cancer (phototherapy)</li> <li>• Serious hypersensitivity (biologic products)</li> <li>• Anti-drug antibodies (biologic products)</li> </ul>	
<p><a href="#"><u>Benefit</u></a></p>	<p>The subject of this NDA, Siliq (brodalumab) is a human monoclonal immunoglobulin (Ig) G2 antibody directed against human interleukin 17 receptor A (IL-17RA). It blocks the biological activities of the pro-inflammatory cytokines IL-17A, IL-17F, IL-17C, IL17A/F heterodimer and IL-25. IL-17 family cytokine concentrations have been reported to be increased in psoriasis.</p> <p>Efficacy was assessed in three pivotal phase 3 trials (Trials 02, 03 and 04). Trial 02 evaluated the efficacy, safety, and effect of withdrawal and retreatment with brodalumab in subjects,</p>	<p>Relative to placebo, Siliq 210 mg every 2 weeks demonstrated superiority on the co-primary endpoints of proportion of subjects with sPGA of 0 or 1 at Week 12 and proportion of subjects with PASI 75 at Week 12, as well as the key secondary endpoints of PASI 100, sPGA of 0, and PSI responder at Week 12.</p> <p>Additionally, relative to ustekinumab, Siliq 210 mg every 2 weeks and weight-</p>

<p>age 18 to 75 years, with moderate to severe plaque psoriasis, randomized 1:1:1 to brodalumab 210 mg every 2 weeks, brodalumab 140 mg every 2 weeks, or placebo. At Week 12, subjects were re-randomized - subjects with success on the sPGA (&lt;2) who were originally randomized to either brodalumab 140 mg or 210 mg were re-randomized 1:1 to continue brodalumab at their induction dose or switch to placebo. All subjects originally randomized to placebo and any subject who did not achieve the sPGA success criterion for re-randomization received treatment with brodalumab 210 mg every 2 weeks. Subjects who experienced “return of disease”, defined as having sPGA ≥3 at or after Week 16 through Week 52, received treatment at his or her initial randomized brodalumab dose, or brodalumab 210 mg every 2 weeks if originally randomized to placebo.</p> <p>Trials 03 and 04 were randomized, double-blind placebo- and active-controlled trials, consisting of two phases – a 12-week placebo- and active-controlled phase and a 52-week active-controlled phase – in adult subjects, age 18 to 75 years, with moderate to severe plaque psoriasis, randomized 2:2:1:1 to brodalumab 210 mg every 2 weeks, brodalumab 140 mg every 2 weeks, ustekinumab, or placebo. At Week 12, subjects were re-randomized - subjects initially randomized to placebo were re-randomized to brodalumab 210 mg every 2 weeks; subjects initially randomized to ustekinumab continued receiving ustekinumab; subjects initially randomized to either of the brodalumab arms were re-randomized to one of the following:</p> <ul style="list-style-type: none"> <li>• Brodalumab 210 mg every 2 weeks</li> </ul>	<p>based Siliq (140 mg every 2 weeks for subjects ≤100 kg; 210 mg every 2 weeks for subjects &gt;100 kg) demonstrated superiority on the primary endpoint of PASI 100 response.</p> <p>Additional analyses assessed brodalumab efficacy by baseline body weight. Brodalumab 210 mg every 2 weeks achieved higher sPGA response rates than brodalumab 140 mg every 2 weeks across most weight subgroups.</p> <p>The treatment effect was generally lower for subjects with a baseline sPGA score of 4 (severe) or 5 (very severe) compared to those subjects with baseline sPGA score of 3 (moderate), although it should be noted that there was only a small number of subjects with sPGA score of 5.</p> <p>Similar results were obtained for PASI 75 response at Week 12 by subgroups of gender, age, race, weight, prior biologic use, and region.</p>
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	<ul style="list-style-type: none"> <li>• Brodalumab 140 mg every 2 weeks</li> <li>• Brodalumab 140 mg every 4 weeks</li> <li>• Brodalumab 140 mg every 8 weeks</li> </ul> <p>For all three trials, the co-primary endpoints, comparing each dose of brodalumab to placebo were:</p> <ul style="list-style-type: none"> <li>• The proportion of subjects with sPGA of 0 or 1 at Week 12</li> <li>• The proportion of subjects with PASI 75 at Week 12,</li> </ul> <p>The secondary endpoints were:</p> <ul style="list-style-type: none"> <li>• The proportion of subjects with PASI 100 at Week 12</li> <li>• The proportion of subjects with sPGA of 0 at Week 12</li> <li>• The proportion of subjects who were Psoriasis Symptom Inventory (PSI) responders defined as having a total score of <math>\leq 8</math>, with each item rated as either 0 (not at all) or 1 (mild) at Week 12.</li> </ul> <p>For Trials 03 and 04, the protocol specified another set of co-primary endpoints for the comparison of brodalumab to ustekinumab:</p> <ul style="list-style-type: none"> <li>• The proportion of subjects with PASI 100 at Week 12 for the comparison of brodalumab 210 mg Q2W vs. ustekinumab.</li> <li>• The proportion of subjects with PASI 100 at Week 12 for the comparison of weight-based dosing (brodalumab 140 mg every 2 weeks for subjects <math>\leq 100</math> kg; brodalumab 210 mg every 2 weeks for subjects <math>&gt; 100</math> kg) vs. ustekinumab.</li> </ul> <p>For the comparison of brodalumab to ustekinumab, the protocol-specified secondary endpoints were:</p> <ul style="list-style-type: none"> <li>• The proportion of subjects with PASI 100 at Week 12 for the comparison of brodalumab 140 mg Q2W vs.</li> </ul>	
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ustekinumab.

- The proportion of subjects with PASI 75 at Week 12 for the comparison of weight-based brodalumab dose vs. ustekinumab.

In the trials, approximately 69% of participants were male, and 91% were Caucasian. The mean age was approximately 45 years. A larger proportion of subjects in Trial 02 had received prior biologic therapy (approximately 46%), compared to 29% and 25% for subjects in Trials 03 and 04, respectively. A larger proportion of subjects in Trial 02 had failed prior biologic therapy (approximately 19%), compared to 13% and 10% for subjects in Trials 03 and 04, respectively. U.S. subjects accounted for 39%, 46%, and 44% of subjects in Trials 02, 03, and 04, respectively.

Both brodalumab 210 mg and 140 mg were superior to placebo at Week 12 for the co-primary endpoints of PASI 75 response and sPGA success, as well as the key secondary endpoints of PASI 100, sPGA of 0, and PSI responder at Week 12 in all three trials. For Trials 03 and 04, brodalumab 210 mg every 2 weeks and the weight-based brodalumab dose were superior to ustekinumab for the primary endpoint of PASI 100 response ( $p < 0.001$  and  $p = 0.0007$ , respectively); however for the comparison of brodalumab 140 mg every 2 weeks versus ustekinumab, only Trial 4 demonstrated statistically significant results ( $p = 0.007$ ); Trial 03 did not demonstrate superiority ( $p = 0.078$ ) for the analysis of PASI 100 response at Week 12. Of note, Trial 03 subjects had a slightly higher mean baseline PASI score of 27 compared to

	<p>the mean baseline PASI score of 20 for Trials 02 and 04 subjects.</p> <p>Additional analyses assessed brodalumab efficacy by baseline body weight. Brodalumab 210 mg every 2 weeks achieved higher sPGA response rates than brodalumab 140 mg every 2 weeks across most weight subgroups.</p> <p>The majority of the subjects enrolled in the trials were Caucasian, and &lt;65 years of age. Therefore, any differences in efficacy for non-Caucasians and the older age (<math>\geq 65</math>) subgroups would be difficult to detect. Similar results were obtained for PASI 75 response at Week 12 by subgroups of gender, age, race, weight, prior biologic use, and region.</p> <p>In all three trials, the treatment effects for sPGA response and PASI 75 were generally consistent across countries, except for the US where sPGA and PASI 75 responses were slightly lower than those of the other countries.</p> <p>In all three trials, the treatment effect was generally lower for subjects with a baseline sPGA score of 4 (severe) or 5 (very severe) compared to those subjects with baseline sPGA score of 3 (moderate). It should be noted that there was only a small number of subjects with sPGA score of 5.</p>	
<p><a href="#">Risk</a></p>	<p>The safety of Siliq was assessed in 4461 patients with moderate-to-severe plaque psoriasis who were exposed to any dose of Siliq, including 4145 who were treated with Siliq for <math>\geq 3</math> months, 3072 subjects who were treated for <math>\geq 12</math> months, 1220 subjects who were treated for <math>\geq 18</math> months,</p>	<p>Suicidal ideation and behavior, including 4 completed suicides, have occurred in subjects treated with Siliq in the psoriasis program, compared with none in the placebo arm. Siliq</p>

	<p>and 102 subjects with follow-up for over 5 years.</p> <p>The review identified the following serious risks:</p> <ul style="list-style-type: none"> <li>• <b>Suicidal ideation and behavior (SIB).</b> There were six completed suicides in the brodalumab clinical study programs: four in the psoriasis studies, one in a rheumatoid arthritis study, and one in a psoriatic arthritis study. All 4 psoriasis subjects who completed suicide were male, between the ages of 39 and 58 years, with body weight ranging from 55 kg to 112 kg, and all received Siliq 210 mg every 2 weeks dosing for various durations. The four suicide events occurred at times ranging from approximately 13 to 120 weeks after the subjects began their Siliq treatment at 210 mg dose and at 14 to 58 days after the subjects received their last 210 mg dose of Siliq.</li> </ul> <p>Based on available PK data, it appears unlikely that the suicidal events could be attributable to high brodalumab exposures in these 4 subjects either throughout the study or at the time of event.</p> <p>While serum levels of IL-17A are higher after receiving brodalumab treatment compared to pre-treatment, a direct correlation between brodalumab treatment-induced up-regulation of serum IL-17A levels and the suicide events was not apparent.</p> <p>The suicide rate in brodalumab trials was 3-4 times</p>	<p>users with a history of suicidality or depression had an approximately 18-fold increase in the incidence of suicidal ideation and behavior than users without such a history.</p> <p>Siliq may increase the risk of infections, including serious infections and fungal infections.</p> <p>Siliq may result in reactivation of latent TB.</p> <p>Siliq can result in worsening of Crohn's disease.</p> <p>The response to live or inactive vaccines in patients treated with Siliq is unknown.</p> <p>Neutropenia, including Grade 3 and 4 neutropenia, has been reported in Siliq-treated patients.</p> <p>Siliq-treated patients can develop anti-drug antibodies. The incidence of Nab could not be accurately determined. A definitive determination of the immunogenicity impacts on PK or efficacy could not be made.</p>
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	<p>higher than in trials of other biologics for psoriasis.</p> <ul style="list-style-type: none"> <li>• <b>Risk of Infection.</b> During the 12-week placebo- and active-controlled period, serious infections occurred in 0.5% of patients in Siliq 210 mg-treated patients versus 0.3% of ustekinumab-treated patients and 0.2% of placebo-treated patients. One case of cryptococcal meningitis occurred with Siliq use and led to discontinuation of therapy.</li> </ul> <p>During the 52-week active-controlled phase, the exposure-adjusted event rates (per 100 subject-years) of serious AEs in the Infections and Infestations SOC were similar between treatment groups, 1.3 for Siliq 210 mg-treated patients versus 1.0 for ustekinumab-treated patients.</p> <ul style="list-style-type: none"> <li>• <b>Risk for Latent Tuberculosis Reactivation.</b></li> <li>• <b>Crohn's Disease.</b> Brodalumab was evaluated in 2 studies of subjects with Crohn's disease, both of which were terminated early due to lack of efficacy, and safety concerns related to worsening of disease. Because worsening of Crohn's disease in subjects with a history of active Crohn's disease is an important identified risk for Siliq, subjects with a known history of Crohn's disease were excluded from the psoriasis clinical trials. In the placebo-controlled phase of the clinical trials, Crohn's disease occurred in one subject in the Siliq group. In the 52-week active-controlled</li> </ul>	<p>Siliq may have an indirect effect on CYP450 enzymes, through modulation of serum levels of cytokines, thus potentially decreasing concentrations of concomitantly administered CYP450 substrates.</p> <p>Reports in the literature suggest a possible role for IL-17 in malignancy risk.</p>
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phase of the clinical trials, a total of 4 AEs for Crohn's disease were reported, all of which occurred in the Siliq treatment group (enteritis =3 and Crohn's=1).

- **Immunizations.**

The review identified the following other adverse reactions:

- **Suicidal Ideation and Behavior.** During the 12-week placebo- and active-controlled phase, 1 subject attempted suicide in the Siliq arm versus none in the comparator arms. During the 52-week active-controlled phase, seven SIB events occurred in the Siliq arm, versus three SIB events in the ustekinumab arm. The follow-up time adjusted incidence rate was 0.2 events per 100 subject-years for Siliq versus 0.4 events per 100 subject-years for ustekinumab. From randomization to end of follow-up, a total of 34 SIB events occurred in the Siliq arm; the follow-up time adjusted incidence rate was 0.37 per 100 subject-years.

In the extended phase of the open-label portion of the clinical trials, Siliq users with a history of depression had an approximately 7-fold increase in SIB incidence than users without a history, and Siliq users with a history of suicidality had an approximately 18-fold increase in SIB incidence than users without a history.

- **Risk of Infection.** During the 12-week placebo-controlled period, Siliq 210 mg-treated and ustekinumab-treated patients had slightly higher rates of infection than placebo-treated patients (25% for Siliq and ustekinumab vs. 23% for placebo), including nasopharyngitis, upper respiratory tract infection, pharyngitis, UTI, bronchitis, and influenza. The Siliq treatment group had a higher rate of fungal infections compared to placebo, 1.8% and 0.9%, respectively. The fungal infections were primarily non-serious skin and mucosal candida infections. Throughout the entire trial, the exposure-adjusted rates for infection were similar between Siliq and ustekinumab.

During the 52-week active-controlled phase, no meaningful increase in infection events occurred, and exposure-adjusted rates were similar between Siliq 210 mg-treated and ustekinumab-treated patients.

- **Neutropenia.** During the 12-week placebo- and active-controlled phase, incidence rates for AEs due to neutropenia were highest in the Siliq 210 mg dose group (1.0%) compared with ustekinumab (0.8%) and placebo (0.5%). There were no post-baseline ANC decreases of grade 4 in the Siliq 210 mg treatment group versus 1 subject in the ustekinumab group. Post baseline ANC decreases of grade 3 were reported for 7 subjects in the Siliq 210 mg group compared with none in placebo- or ustekinumab-treated subjects.

Through the 52-week active-controlled phase, the exposure-adjusted events rates (per 100 subject-years) for neutropenia were similar between Siliq-treated subjects and ustekinumab-treated subjects. During the 52-week active-controlled phase, decreases in ANC of grade 4 were reported for 4 Siliq-treated subjects (0.1%) compared with 1 ustekinumab-treated subject (0.2%). Post baseline ANC decreases of grade 3 were reported for 0.4% of Siliq-treated subjects and 0.2% of ustekinumab subjects.

- **Immunogenicity.** Following up to 52 weeks of treatment, 2.7% (120/4447) of subjects with psoriasis treated with Siliq developed ADA across seven clinical trials; and 2.1% (86/4058) of subjects developed ADA in Phase 3 trials. Of the subjects who developed ADA, none were positive for neutralizing antibodies. However, the incidence of neutralizing antibody development could be underestimated because the assay had limitations in detecting neutralizing antibodies in the presence of brodalumab. A definitive determination of the immunogenicity impacts on PK or efficacy could not be made because of the large variability in brodalumab trough concentrations and the small number of subjects who developed ADA in psoriasis clinical trials.

The most common adverse reactions reported in at least 1% of patients receiving Siliq through week 12, and occurring

	<p>with greater frequency than with placebo treatment were headache, arthralgia, fatigue, oropharyngeal pain, diarrhea, nausea, myalgia, influenza, injection site reaction, neutropenia and tinea infections.</p> <p>Brodalumab co-administration increased the exposure of midazolam (a CYP3A4 substrate) in subjects with psoriasis.</p> <p>In general, elevated levels of pro-inflammatory cytokines occur in inflammatory conditions. These pro-inflammatory cytokines reportedly suppress some CYP450 enzymes, resulting in elevated CYP450 substrate exposures. Effective treatments for inflammatory conditions are expected to reduce the level of pro-inflammatory cytokines, thus indirectly modulating CYP450 enzyme activity and decreasing CYP450 substrates, potentially resulting in a loss of efficacy.</p> <p>Conflicting reports in the literature exist over the association between IL-17 and malignancy risk.</p>	
<p><u>Risk Management</u></p>	<ol style="list-style-type: none"> <li>1. SIB</li> <li>2. Infections</li> <li>3. Risk for Latent Tuberculosis Reactivation</li> <li>4. Crohn's Disease</li> <li>5. Immunizations</li> <li>6. Neutropenia</li> <li>7. Immunogenicity</li> <li>8. CYP450 substrates</li> <li>9. Potential for increased risk of malignancy</li> </ol>	<ol style="list-style-type: none"> <li>1. A Boxed Warning will convey the increased risk of SIB observed with Siliq treatment. The product will also be designated for second-line treatment, after failure or loss of response to other systemic therapies. Labeling will also convey that the product should be discontinued if an adequate response is not achieved within 12-16 weeks. A REMS will be required</li> </ol>

		<p>to ensure that patients and prescribers are fully informed of the SIB risk. The REMS will consist of a one-time prescriber enrollment (acknowledging understanding of the SIB risk and agreeing to counsel patients on the risk), a one-time patient enrollment (an agreement form acknowledging receipt of counseling on SIB risk and an understanding of the risk), and a one-time pharmacy certification (to ensure that prescribers are certified and patients are enrolled).</p> <p>2. The W&amp;P section of labeling will recommend that for patients who develop a serious infection or are not responding to standard therapy, prescribers should discontinue Siliq.</p> <p>ARIA will be used for surveillance of post-marketing occurrences of serious infections (broadly defined).</p> <p>Post-marketing data on the occurrence of opportunistic fungal infections will be collected in the required observational study of malignancy with Siliq.</p>
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		<p>3. The W&amp;P section of labeling will recommend that patients be evaluated for tuberculosis (TB) infection prior to initiating treatment with Siliq. Patients with latent TB should be treated prior to initiating Siliq. Patients receiving Siliq should be monitored for signs and symptoms of active TB during and after treatment. Patients with active TB infection should not receive Siliq.</p> <p>Post-marketing data on the occurrence of TB infections will be collected in the required observational study of malignancy with Siliq.</p> <p>4. Labeling will contraindicate the use of Siliq in patients with Crohn's disease, and recommend discontinuing Siliq in patients who develop Crohn's disease during Siliq treatment.</p> <p>5. The W&amp;P section of labeling will recommend that use of live vaccines in patients treated with Siliq should be avoided.</p> <p>6. Information on the occurrence of neutropenia in the clinical trials will</p>
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		<p>be conveyed in the Adverse Reactions section of labeling.</p> <p>ARIA will be used to collect post-marketing data on cases of hospitalized neutropenia. Post-marketing data on the occurrence of neutropenia will be collected in the required observational study of malignancy with Siliq.</p> <p>7. Information on the development of anti-drug antibodies and neutralizing antibodies (NAb) in the clinical trials will be conveyed in the Adverse Reactions section of labeling. The limitation of the assay in the detection of NAb in the presence of brodalumab, and the likely under-ascertainment of the presence of NAb in the clinical trials will be conveyed in product labeling.</p> <p>8. The Drug Interactions section of labeling will recommend that upon initiation or discontinuation of Siliq in patients who are receiving concomitant drugs which are CYP450 substrates, particularly those with a narrow therapeutic index, monitoring for effect (e.g.,</p>
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		<p>warfarin) or drug concentration (e.g., cyclosporine) should be considered, and dose modification of the CYP450 substrate should also be considered.</p> <p>9. Section 13 of product labeling will convey the potential effect of brodalumab on malignancy risk, based on review of the published literature.</p> <p>The applicant will be required to conduct a prospective, observational study to assess the long-term safety of Siliq compared to other therapies used in the treatment of adults with moderate-to-severe plaque psoriasis on the primary outcome of malignancy.</p> <p>Additionally, the applicant has proposed enhanced pharmacovigilance (EPV) for the following Adverse Events of Special Interest:</p> <ul style="list-style-type: none"><li>• Suicidal Ideation and Behavior (SIB)</li><li>• Cardiovascular Events/Major Adverse Cardiac Events (MACE)</li><li>• Infections</li><li>• Crohn's Disease</li></ul>
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		<ul style="list-style-type: none"><li>• Neutropenia</li><li>• Hypersensitivity</li><li>• Malignancy</li></ul> <p>They plan to use targeted follow up questionnaires for all cases of:</p> <ul style="list-style-type: none"><li>• SIB</li><li>• Cardiovascular Events/MACE</li></ul> <p>FDA's Division of Pharmacovigilance has provided modifications to the applicant's protocol to improve the adequacy of the proposed EPV.</p>
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## **Other Background**

### **Regulatory History**

IND (b) (4) was opened August 27, 2009.

In March 2011, a Guidance meeting was conducted.

No formal End of Phase 2 meeting was conducted for this application. No Special Protocol Assessment was requested or provided for any of the Phase 3 trials. However, the Agency provided comments regarding the assessment of consistency in treatment effects across sites, secondary endpoints, primary analysis method, method for handling missing data, and sample size calculation in advice letters dated November 6, 2011 and June 6, 2012. The protocol for Trial 02 was amended three times (7/17/2012, 10/17/2013, and 3/26/2014), and the protocols for Trial 03 and 04 were amended three times (5/31/2012, 10/17/2013, 3/26/2014) with an additional amendment for Trial 03 (11/11/2014). The last revision for Trial 03 pertained to the long-term extension period.

In March 2015, a pre-BLA meeting was held with Amgen, the original sponsor of the IND.

Following the May 2015 meeting with Amgen to discuss the Suicidal Ideation and Behavior (SIB) risk across the brodalumab program, Amgen decided to discontinue further development of brodalumab and terminated all ongoing studies.

In October 2015, another pre-BLA meeting was held with a new sponsor, Astra Zeneca, to discuss the Agency's concern regarding the SIB observed in the brodalumab clinical development program.

In November 2015, BLA 761032 was submitted to the Agency. The BLA was given a standard review timeline with a PDUFA date of November 16, 2016.

In April 2016, the Agency received notification that the BLA had been transferred to Valeant Pharmaceuticals Luxembourg.

On October 18, 2016 the Agency received a major amendment (a proposed REMS with ETASU), extending the PDUFA goal date to February 16, 2017.

Brodalumab received approval for marketing in Japan on July 4, 2016, for psoriasis. An application to the EMA is pending, with action anticipated by the first quarter of 2017.

### **Product Quality**

There are no product quality issues that preclude approval.

OPQ concluded that the manufacturing control strategy coupled with in-process, release, and stability testing will ensure process consistency and drug substance and drug product that have appropriate quality attributes and are free of adventitious agents.

The review of the assays used to evaluate the immunogenicity rates in the clinical trials indicated that the neutralization assay was not tolerant to the levels of brodalumab present in the clinical study serum samples. This will be conveyed in product labeling.

The dating period for brodalumab drug product, 210 mg/1.5 mL, shall be 12 months from the date of manufacture when stored at 2° to 8°C. The date of manufacture shall be defined as the date of final sterile filtration of the formulated drug product.

The dating period for brodalumab drug substance shall be (b)(4) months from the date of manufacture when stored at (b)(4)°C.

A claim for categorical exclusion under 21 CFR 25.31 (c) and 21 CFR 25.34 (b) was accepted.

The drug substance and drug product parts of BLA 761032 were reviewed from a microbial control, sterility assurance and microbiology product quality perspective. No approvability issues were identified. The applicant has agreed to a PMC “to perform 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.”

The Office of Process and Facilities made a final overall manufacturing inspection “approval” recommendation for the facilities involved in this application.

### **Non-clinical Pharmacology/Toxicology**

There are no pharmacology/toxicology issues that preclude approval.

In cynomolgus monkeys dosed with 0, 10, 25 or 90 mg/kg/dose SC brodalumab weekly for six months, mild skin changes and histopathology (mid-dose [MD] and high-dose [HD]), increased neutrophil counts (HD) and decreased albumin/globulin ratios (MD and HD) were observed. These changes were at least partially reversible during the recovery period. The NOAEL was determined to be 90 mg/kg/dose.

Pregnant cynomolgus monkeys were administered weekly SC injections of brodalumab (0, 25, 90 mg/kg) from gestational day 20 to parturition to evaluate potential adverse effects of brodalumab on the pregnant female and on development of the infant. No dam died during this study, and no brodalumab-related abnormalities were observed in infants. However, maternal brodalumab treatment was associated with neonatal deaths (25, 90 mg/kg) and maternal neglect (90 mg/kg). Under the experimental conditions, a NOAEL for prenatal and postnatal development could not be determined.

Based on ICH S6 guidelines, no genetic toxicology studies were conducted with brodalumab.

No carcinogenic concerns exist related to the structure or metabolism of brodalumab. As a monoclonal antibody, brodalumab would not be expected to be able to enter the nucleus and interact with DNA. It will be catabolized to peptides and constituent amino acids via normal metabolic pathways.

Due to conflicting reports in the literature over the role of IL-17 and malignancy, the non-clinical reviewer has recommended postmarketing surveillance of malignancy report frequency compared to background rates to provide a determination of potential cancer risk for brodalumab.

Anti-drug antibodies (ADAs) occurred in 69% of adult female low-dose (LD) and HD animals on at least one time point. Of those who were ADA positive, 29% also tested positive for the presence of anti-brodalumab neutralizing antibodies. Among infant animals, 29% in the brodalumab-exposed groups tested positive for ADAs; 33% of those ADA positive animals also tested positive for anti-brodalumab neutralizing antibodies. The mothers of all anti-brodalumab positive infant animals tested positive for ADAs. ADAs were also detected in the control group - 44% of adult female animals tested positive for ADAs on at least 1 time point during the study, and 13% of those also tested positive for anti-brodalumab-neutralizing antibodies. Forty-five percent of infant animals tested positive for ADAs, all of whom were born to ADA positive mothers. The time course and magnitude of the antibody responses are consistent with an immune response. The applicant believes that brodalumab in the serum at concentrations  $\geq 1.56$   $\mu\text{g/mL}$  may have interfered with the detection of anti-brodalumab neutralizing antibodies in the bioassay.

### **Clinical Pharmacology**

There are no clinical pharmacology issues that preclude approval.

Based on population PK modeling, the estimated brodalumab bioavailability was approximately 55%.

Following multiple subcutaneous doses of 210 mg every 2 weeks, the mean ( $\pm$ SD) peak serum concentrations ( $C_{\text{max}}$ ) at steady-state was  $20.6 \pm 14.6$  mcg/mL, observed 3 days post-dose. The mean ( $\pm$ SD)  $\text{AUC}_{\text{tau}}$  over the two-week dosing interval was  $227 \pm 167$  mcg•day/mL. The median time to maximum brodalumab concentration ( $T_{\text{max}}$ ) was 3.0 days (range: 2.0 to 4.0 days).

Based on population PK model-based simulations, serum brodalumab concentration would drop below the assay quantification limit 63 days after discontinuation of brodalumab 210 mg every 2 weeks.

Brodalumab clearance and volume of distribution increase as body weight increases. However, the Siliq 210 mg dose consistently achieved greater response rates at Week 12 and 52 than the 140 mg dose both in subjects with body weight >70 kg, as well as in subjects with body weight ≤70 kg. Therefore, the Applicant’s proposed dosing regimen (210 mg at Weeks 0, 1, 2, followed by every 2 week dosing), regardless of weight, is supported.

The exposure of midazolam, a CYP3A4 substrate, was increased by 24% in subjects with plaque psoriasis one week following a single subcutaneous administration of 210 mg brodalumab (N.B. the T<sub>max</sub> of brodalumab is 3 days). Clinical studies with substrates of other CYP450 isozymes have not been conducted.

The PK comparability between the to-be-marketed and phase 3 pre-filled syringe presentations was adequately demonstrated.

The maximal effect of Siliq on sPGA of 0 or 1 was achieved by week 12, with some gain in responders with treatment from week 12 to week 16, but limited probability of becoming a responder beyond week 16.

LOCF	Visit	sPGA(0,1) responder		Change in response	
		No	Yes	No-->Yes (gained response)	Yes-->No (lost response)
Pooled Studies 03 & 04	Week 12	68	271		
	Week 16	58	281	22 (6%)	12
	Week 20	23	269	7 (2%)	17
	Week 24	20	261	4 (1%)	12
Study 03	Week 12	34	134		
	Week 16	22	146	14 (8%)	2
	Week 20	15	133	2 (1%)	13
	Week 24	12	128	2(1%)	7
Study 04	Week 12	34	137		
	Week 16	36	135	8 (5%)	10
	Week 20	8	136	5 (3%)	4
	Week 24	8	133	2 (1%)	5

**Immunogenicity.** Following up to 52 weeks of treatment, 2.7% (120/4447) of subjects with psoriasis developed brodalumab treatment-emergent ADA across seven clinical trials; and 2.1% (86/4058) of subjects developed brodalumab treatment-emergent ADA in Phase 3 trials. The antidrug antibody (or binding antibody) assay performance was acceptable, whereas the neutralizing antibody assay had limitations in detecting neutralizing antibodies in the presence of brodalumab. Of the subjects who developed ADA, none (0%) were classified as positive for neutralizing antibodies. However, the incidence of neutralizing antibody (Nab) development could be underestimated because the assay used to test for Nab has limitations in detection in the presence of brodalumab.

At Week 52, a trend of numerically lower response rates was observed in ADA positive subjects when compared to ADA negative subjects in the phase 3 trials. A definitive determination of the immunogenicity impacts on PK or efficacy could not be made because of the large variability in

brodalumab trough concentrations and the small number of subjects who developed ADA in the trials.

***Effect of age, sex, or race.*** Age, sex, or race did not significantly influence the PK of brodalumab.

***Renal impairment.*** No formal studies were conducted in subjects with renal impairment. Brodalumab is a human monoclonal antibody with molecular size of approximately 144 kDa; therefore, it is unlikely for intact brodalumab to be filtered by the kidneys or excreted in urine.

***Hepatic impairment.*** No formal studies were conducted in subjects with hepatic impairment. Metabolism by CYP enzymes or secretion into bile is generally not a significant contributor to the elimination of IgG antibodies such as brodalumab.

### **Clinical/Statistical - Efficacy**

***Pivotal trials.***

The table below provides a summary of the efficacy results from the pivotal trials.

**Table 2. Proportion of Subjects Achieving Treatment Success at Week 12 for Trials 02, 03, and 04**

		Brodalumab 210 mg	Brodalumab 140 mg	Placebo	Ustekinumab	Weight- based <sup>(1)</sup> brodalumab
Trial 02		N=222	N=219	N=220	N/A	N/A
	sPGA of 0 or 1	168 (76)	118 (54)	3 (1)		
	PASI 75	185 (83)	132 (60)	6 (3)		
	PASI 100	93 (42)	51 (23)	1 (0.5)		
	sPGA of 0	93 (42)	51 (23)	1 (0.5)		
	PSI responder <sup>(2)</sup>	136 (61)	116 (53)	9 (4)		
Trial 03		N=612	N=610	N=309	N=300	N=610
	sPGA of 0 or 1	481 (79)	354 (58)	12 (4)	183 (61)	420 (69)
	PASI 75	528 (86)	406 (67)	25 (8)	210 (70)	470 (80)
	PASI 100	272 (44)	157 (26)	2 (1)	65 (22)	205 (34)
	sPGA of 0	274 (45)	157 (26)	2 (1)	65 (21)	205 (34)
	PSI responder	414 (68)	314 (52)	21 (7)	166 (55)	372 (61)
Trial 04		N=624	N=629	N=315	N=313	N=628
	sPGA of 0 or 1	497 (80)	377 (60)	13 (4)	179 (57)	430 (69)
	PASI 75	531 (85)	435 (69)	19 (6)	217 (69)	484 (77)
	PASI 100	229 (37)	170 (27)	1 (0.3)	58 (19)	191 (30)
	sPGA of 0	229 (37)	170 (27)	1 (0.3)	58 (19)	191 (30)
	PSI responder	382 (61)	336 (53)	20 (6)	162 (52)	373 (59)

Source: reviewer table; analysis was based on the Intent to Treat (ITT) set defined as all randomized subjects. Missing data was imputed using non-responder imputation (NRI).

(1) Weight-based: Brodalumab 140 mg for subjects ≤100 kg; brodalumab 210 mg for subjects >100 kg.

(2) PSI responder is defined as total score ≤ 8, with no item score > 1 at Week 12.

The protocol specified using the Cochran Mantel Haenszel (CMH) test stratified by baseline body weight (≤100 kg vs. >100kg), prior biologic use (yes, no), geographic region, and baseline value of the endpoint (≤ median, >median for PASI, 3, 4, 5 for sPGA).

The Office of Scientific Investigations (OSI) conducted inspections of three clinical investigator sites. OSI concluded that “The study appears to have been conducted adequately, and the data generated by these sites appear acceptable in support of the respective indication.”

### **Advisory Committee**

An Advisory Committee was convened on July 19, 2016 to discuss the efficacy, safety, approvability, and potential post-approval risk mitigation strategies for brodalumab for the treatment of moderate to severe plaque psoriasis. The committee was asked to vote on the following question:

Is the overall benefit/risk profile of brodalumab acceptable to support approval for the treatment of moderate to severe plaque psoriasis in adult patients who are candidates for systemic therapy or phototherapy.

- a. Yes, with labeling alone to manage the risks
- b. Yes, but only if certain risk management options for SIB beyond labeling are implemented
- c. No

Please provide a rationale for your vote. If you voted for A, please describe the labeling you would recommend to manage the risks. If you voted for B, describe the interventions or tools you believe would help mitigate the risk of SIB, in addition to labeling.

The committee voted 4 for 'a', 14 for 'b' and 0 for 'c'. Four members (Waters, Smith, Tan, and Bigby) recommended a boxed warning for the risk of suicidality. The committee was divided on the need for a registry to further characterize the risk of suicidality, and if needed, whether the registry should be voluntary or mandatory. The committee acknowledged the efficacy of the product and the need to have additional highly effective therapies available to patients.

#### **Risk Evaluation and Mitigation Strategies (REMS) Oversight Committee (ROC)**

ROC meetings to discuss the brodalumab application were held on May 25, 2016 and August 9, 2016. The initial meeting was to reach agreement on potential strategies to mitigate the risk for suicidality, for presentation at the July 19, 2016 AC meeting. The follow-up meeting was held to gain concurrence from the ROC, and the CDER director, on whether brodalumab could be approved with post-marketing strategies to mitigate the risk of suicidality. The ROC acknowledged the seriousness of psoriasis, the availability of alternative treatments with comparable efficacy to brodalumab, and the presence of a potentially fatal risk observed in the clinical development program, which may or may not be real. The ROC recommended that if brodalumab were to be approved, it should have a restrictive program, consisting of a Boxed Warning; use of the product in patients who have failed to respond or lost response to other biologic therapies; a recommendation to discontinue treatment if an adequate response has not been achieved within 12 to 16 weeks; and a REMS with ETASU to include physician certification, pharmacy certification, and safe use conditions (a patient acknowledgement form). The ROC also recommended a post-marketing required trial to prove that brodalumab's safety profile is not "unacceptably worse" than available treatments.

#### **Pregnancy Considerations**

Consistent with the Pregnancy and Lactation Labeling Rule guidelines, The **Use in Specific Populations** section, **Pregnancy** subsection, of the product label will state that there are no available data on Siliq use in pregnant women.

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).

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.

### **Pediatrics**

Brodalumab was discussed at a July 6<sup>th</sup>, 2016 meeting of the Pediatric Review Committee (PeRC). PeRC concurred with the plan for a partial waiver in patients less than 6 years of age because studies are impossible and highly impractical, and to consider waiver/deferral of studies in older patients after the AC has convened.

***Pediatric Use.*** The **Use in Specific Populations** section, **Pediatric Use** subsection, of the product label will state that the safety and effectiveness of Siliq have not been evaluated in pediatric patients.

***Required Pediatric Studies.*** An agreed iPSP letter was issued on January 15, 2015, in which the Agency agreed with the applicant's plan to request a waiver for subjects 0 to less than 6 years of age and to defer the PSP in subjects 6 to less than 17 years of age until such time as adult safety experience can be evaluated.

### **Other Relevant Regulatory Issues**

#### **Tradename Review**

The applicant's proposed tradename "Siliq" is acceptable. The applicant was informed of this determination on March 16, 2016.

#### **Consults**

##### **Division of Biometrics VII (DB VII)**

DB VII was consulted to assess the safety signals of suicidal ideation and behavior (SIB) and major adverse cardiovascular events (MACE). DB VII found: "In total, 35 SIB events occurred in 4464 brodalumab users (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). The incidence of MACE among 4273 subjects exposed to brodalumab was 1.1% (95% CI: 0.83–1.49) and the follow-up adjusted incidence rate was 0.6 per 100 subject-years (95% CI: 0.42–0.76). The subgroup analysis of SIB incidence rate by history of suicidality resulted in a 12–18 fold increase among subjects with a history compared to those without. Similarly, the subgroup analysis of MACE incidence rate by (1) history of ischemic heart disease and (2) history of cardiac or vascular

disorder yielded a 9-fold and 4.7-fold increase, respectively, among subjects with a history compared to those without.

The placebo-controlled phase was only 12 weeks. Therefore the exposure time was not long enough to observe or compare SIB and MACE between brodalumab and placebo. Additionally, the sponsor terminated the clinical programs prematurely. This limited our ability to assess the association between SIB and MACE and the use of brodalumab.”

### **Division of Cardiovascular and Renal Products (DCRP)**

DCRP was consulted to review MACE data in the brodalumab clinical trials, to determine if there was a credible safety signal for MACE. DCRP concluded “Evidence from the brodalumab development program does not establish an elevated risk of MACE, and the risk of MACE should not influence regulatory decision making.”

### **Clinical Outcome Assessment (COA)**

COA was consulted to review the patient reported outcome (PRO) assessment used in the three phase 3 brodalumab clinical trials, the Psoriasis Symptom Inventory (PSI), to determine its adequacy to support the applicant’s labeling claim. COA concluded that “the evidence submitted by the applicant sufficiently demonstrates that PSI is a well-defined and reliable assessment and fit-for-purpose in the context of this particular drug development program to assess the signs and symptoms of psoriasis in pivotal trials. Furthermore, PSI is adequate to support a labeling claim related to improvement in psoriasis signs and symptoms (i.e., itching, redness, scaling, burning, stinging, cracking, flaking, and pain).”

### **Office of Surveillance and Epidemiology (OSE), Office of Pharmacovigilance and Epidemiology (OPE), Division of Epidemiology I (DEPI I)**

#### ***Suicidal Ideation and Behavior (SIB)***

DEPI I was consulted to evaluate data on SIB events in brodalumab clinical trials, and to summarize available information on suicide rates in psoriasis patients treated with biologics in clinical trials. DEPI I concluded:

- 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.*
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 CFR 313.125(b)(4) [sic].”

DEPI I did not recommend the collection of postmarketing observational data, given the limitations of such data for suicidal outcomes.

### ***Infections***

DEPI I was consulted 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. DEPI I concluded that “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 applicant 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.”

### ***Major Adverse Cardiovascular Events (MACE)***

DEPI I was consulted to evaluate data on MACE in brodalumab clinical trials, and to summarize available information on MACE in psoriasis clinical trials with other biologics. DEPI I concluded that “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.”

## **Division of Psychiatry Products (DPP)**

DPP was consulted 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. DPP concluded that no definitive conclusion regarding the relationship between brodalumab and suicidality could be made due to the short duration of the placebo-controlled phase of the clinical trials, and the use of different scales and adjudication methods during different phases of the clinical trials to detect and classify SIB events. DPP also expressed concern over the inability of pharmacovigilance methods to detect events during the postmarketing period, and whether any proposed REMS would be helpful in preventing suicides. DPP recommended a pre-approval “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.”

**Office of the Commissioner, Office of Good Clinical Practice (OGCP) and Office of Pediatric Therapeutics (OPT)**

OGCP and OPT were consulted to address the use of a mandatory versus a voluntary registry to assess risk for suicide ideation and behavior as part of post-marketing management. OGCP and OPT concluded:

*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.*

**Center for Devices and Radiological Health (CDRH), Office of Compliance (OC), Division of Manufacturing & Quality (DMQ), Respiratory, ENT, General Hospital, Ophthalmic Device Branch (REGO)**

CDRH was consulted to provide an evaluation of the device constituent part of the brodalumab pre-filled syringe (PFS). CDRH concluded that there were no outstanding device issues, and recommended BLA approval of the device constituent part of the brodalumab PFS.

CDRH was also asked to evaluate the applicant’s compliance with applicable Quality System Requirements for the approvability of BLA 761032. CDRH/OC determined that the BLA could

be approved. No inspection was required as the facility responsible for the final assembly and packaging of the final combination product had been inspected within the last two years, and the inspection was acceptable.

#### **Division of Medical Policy Programs (DMPP)/Office of Prescription Drug Promotion (OPDP)**

OPDP reviewed the Package Insert (PI) and Carton and Container Labeling for Siliq. OPDP had no comments regarding the proposed Carton and Container Labeling. OPDP provided recommendations to improve consistency throughout the PI and to avoid promotional statements.

OPDP and DMPP reviewed the Medication Guide (MG) and Instructions for Use (IFU). In their collaborative review, they simplified wording and clarified concepts where possible, ensured that the MG and IFU were consistent with the Prescribing Information (PI), removed unnecessary or redundant information, ensured that the MG and IFU were free of promotional language or suggested revisions to ensure that it was free of promotional language, ensured that the MG met the Regulations as specified in 21 CFR 208.20, and ensured that the MG and IFU met the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information.

#### **Division of Medication Error, Prevention, and Analysis (DMEPA)**

DMEPA was consulted to review the applicant's Human Factors (HF) validation study report, the proposed carton and container labeling, prescribing information (PI), and Instructions for Use (IFU). DMEPA found the HF validation study results acceptable. DMEPA identified areas for improvement with regard to the product strength display on the carton and container labels, as well as other aspects of the labels and labeling that needed revision to improve readability of important information and promote safe use of the product.

#### **Division of Pediatric and Maternal Health (DPMH)**

DPMH reviewed the available relevant pregnancy and lactation data and recommended the following language for section 8.2 of the PI: *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.*

DPMH proposed a postmarketing requirement to perform a pregnancy exposure registry study and a complementary study to assess the safety of Siliq in pregnant women.

DPMH restructured the Siliq label to be consistent with the PLLR guidelines.

#### **Division of Risk Management (DRISK)/Risk Evaluation and Mitigation Strategies (REMS)**

DRISK provided a consultative review on the applicant's proposed REMS with ETASU. In their draft review dated December 12, 2016, DRISK provided revisions to the applicant's proposed REMS document and REMS appended materials, and advised the applicant to submit a REMS website and revised REMS supporting document, including the REMS assessment plan. Finalization of the REMS materials are pending at this time.

### **Division of Pharmacovigilance**

DPV reviewed the applicant's draft protocol "Proposed Enhanced Pharmacovigilance Plan for Siliq", which included targeted follow-up questionnaire forms for Cardiovascular Adverse Events of Special Interest and Suicidal Ideation and Behavior. DPV provided modifications to the protocol, and further asked that the applicant "provide an estimate of drug utilization data based on patient-level exposures, stratified by patient age, including an estimate of person-years and number of individual patients exposed in each Periodic Report."

### **Postmarketing Requirements and Commitments**

#### *Post Marketing Requirements*

- PMR 1:** Conduct a retrospective cohort study using administrative databases to identify pregnancy outcomes in a cohort of women with a diagnosis of psoriasis exposed to brodalumab versus a non-brodalumab systemic medication exposure cohort. The outcomes will include major congenital malformations, spontaneous abortions, stillbirths, and small for gestational age births. This study may use multiple data sources in order to obtain a sufficient sample size as women with psoriasis are counseled to avoid systemic treatments while trying to conceive and during the course of pregnancy.
- PMR 2:** Conduct a prospective, registry-based observational exposure cohort study that compares the maternal, fetal, and infant outcomes of women with the diagnosis of psoriasis exposed to brodalumab 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 births, 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.
- PMR 3:** Open-label study to determine PK of a single dose of brodalumab in 16 children (b) (4) o < 18 years old) with severe plaque psoriasis.
- PMR 4:** Double-blind, active comparator-controlled, multicenter study with brodalumab to determine the safety and efficacy in adolescent subjects (12 to < 18 years old) with severe plaque psoriasis.

- PMR 5:** Open label, single arm study with brodalumab to determine safety and efficacy in children (b)(4) to <12) with severe plaque psoriasis.
- PMR 6:** 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) 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.

#### *Post Marketing Commitments*

- PMC 1:** 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.

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/s/  
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AMY G EGAN  
12/28/2016