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RESEARCH**

APPLICATION NUMBER:

761032Orig1s000

SUMMARY REVIEW

Division Director Summary Review for Regulatory Action

Date	(electronic stamp)
From	Kendall A. Marcus, MD
Subject	Division Director Summary Review
BLA #	761032
Applicant	Valeant Pharmaceuticals North America LLC
Date of Submission	November 16, 2015
PDUFA Goal Date	February 16, 2017 (Amended PDUFA goal date after receipt of major amendment on October 18, 2016)
Proprietary Name / Non-Proprietary Name	Siliq (brodalumab)
Dosage Form(s) / Strength(s)	Single-dose prefilled syringe for subcutaneous injection/210 mg of brodalumab in 1.5 mL solution (140 mg/mL)
Applicant Proposed Indication(s)/Population(s)	The treatment of moderate to severe plaque psoriasis in adult patients who are candidates for systemic therapy or phototherapy
Action/Recommended Action for NME:	Approval with a REMS with ETASU and labeling to include a Boxed Warning for risk of suicide behavior
Approved/Recommended Indication/Population(s) (if applicable)	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

Material Reviewed/Consulted	Names of discipline reviewers
OND Action Package, including:	
Medical Officer Review	Gary Chiang, MD, MPH
Statistical Review	Carin Kim, PhD
Pharmacology Toxicology Review	Carmen Booker, PhD
OPQ Review	Qing Zhou, PhD
Clinical Pharmacology Review	Jie Wang, PhD
Pharmacometrics Review	Dhananjay Marathe, PhD
Division of Biostatistics VII	Ling Lan, PhD
DPP	Jean Kim, MD, MA
OSE/DPV	Bob Levin, MD
OSE/DEPI I	Andrew Mosholder, MD, MPH; Gabriella Anic, PhD, MPH
OSE/DRISK	Erin South, PharmD

OSE/DMEPA	Carlos Mena-Grillasca, RPh
DPMH	Christos Mastroyannis, MD
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COA	Yasmin Choudry, MD
OSI	Roy Blay, PhD
DCRP	Senatore Fortunato, MD
CDTL	David Kettl, MD

OND=Office of New Drugs
 OPQ=Office of Pharmaceutical Quality
 OPDP=Office of Prescription Drug Promotion
 OSI=Office of Scientific Investigations
 CDTL=Cross-Discipline Team Leader
 OSE= Office of Surveillance and Epidemiology
 DEPI= Division of Epidemiology
 DMEPA=Division of Medication Error Prevention and Analysis
 DRISK=Division of Risk Management

Benefit-Risk Summary and Assessment

The subject of this application, Siliq (brodalumab), is a human IgG2 monoclonal antibody which binds to the human interleukin-17 receptor A (IL-17RA) and blocks the biologic activities of IL-17A, IL-17C, IL-17F, IL-17A/F heterodimer and IL-25. IL-17A is a naturally occurring cytokine that is involved in normal inflammatory and immune responses and also plays a role in the pathogenesis of plaque psoriasis. Siliq (brodalumab) drug product is supplied at 210 mg/1.5 mL as a sterile, single-dose, preservative-free solution for injection in a pre-filled syringe (PFS). The recommended dose is 210 mg every 2 weeks (Q2W).

There are currently ten approved systemic therapies for psoriasis patients with moderate to severe disease who are candidates for systemic therapy. Available biologic products include the TNF blockers (etanercept, adalimumab, infliximab), an IL-12/23 blocker (ustekinumab), and the recently approved IL-17 blockers (secukinumab and ixekizumab). Available drug products include acitretin, methotrexate, cyclosporine and apremilast. Efficacy of these products is variable and none work for all who use them. Patients with psoriasis on the more severe end of the spectrum tend to have unremitting disease requiring continuous treatment; those using systemic agents generally experience a waning of treatment effect over time. Consequently, few of them can remain on one therapy over the course of their disease. Also of note, all of the currently available therapies have potentially significant risks associated with their use. Clearly, additional therapies are needed to treat psoriasis.

To support an efficacy claim for Siliq (brodalumab) for the treatment of psoriasis, the applicant submitted results from three Phase 3 randomized, double-blind, placebo-controlled clinical trials. All three trials included a placebo arm and two trials included an ustekinumab active comparator arm. These trials convincingly demonstrated substantial efficacy of brodalumab on the two co-primary endpoints at the primary time point of Week 12; about 80% of enrolled subjects achieved success in both a reduction of the static Physician Global Assessment score (sPGA) to "clear" or "almost clear" (sPGA 0 or 1) and a 75% reduction in Psoriasis Area and Severity Index score (PASI 75). Of note, about 40% of subjects also experienced complete clearance (PASI 100) of their psoriasis at Week 12. 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. In this analysis, PASI-90 and PASI-100 response rates were 65% and 35%, respectively.

In certain aspects, the safety profile of brodalumab for the treatment of adult patients with moderate-to-severe plaque psoriasis appears to be similar to that of other approved systemic biologic therapies for this disease. Infections, including serious infections, and development or worsening inflammatory bowel disease were reported with brodalumab therapy. These are known and potentially serious adverse reactions associated with other approved systemic biologic therapies for psoriasis patients. These reactions will be included in the Warnings and Precautions section of product labeling. In addition, the risk of latent TB reactivation, and the need to avoid live vaccines and to complete immunizations prior to initiating brodalumab will be included in the Warnings and Precautions section, consistent with labeling for approved systemic biologic therapies.

Adverse drug reactions (ADRs) that occurred with a $\geq 1\%$ overall incidence rate in brodalumab-treated subjects and more frequently than in the placebo group were headache, arthralgia, fatigue, oropharyngeal pain, influenza, diarrhea, nausea, myalgia, injection site reactions, neutropenia and tinea infections. ADRs identified in the applicant's review through Week 12 across all psoriasis studies that occurred in $< 1\%$ of brodalumab-treated subjects included conjunctivitis and candida infections. Adverse events that were reported as the reason for study discontinuation in more than one brodalumab-treated subject were neutropenia, arthralgias and urticaria.

A unique safety concern that emerged during the development program was suicidal ideation and behavior (SIB), and more specifically, the observed incidence of completed suicide. Six completed suicides were reported during the conduct of the brodalumab development program, including four (0.09% of enrolled subjects) that occurred in the psoriasis clinical trials. The rate of suicide observed in this program is higher than expected when compared to the numbers of suicides observed in other development programs enrolling similar populations. These types of crude cross-study comparisons are problematic and limited by a number of factors, including heterogeneity in patient characteristics, follow-up methods, and ascertainment of SIB events. None-the-less, as noted in the cross-disciplinary team leader (CDTL) memo, this number of suicides in a psoriasis development program is unprecedented.

The primary clinical reviewer for the Division of Dermatology and Dental Products (DDDP), as well as consultative reviews from the Division of Psychiatry Products (DPP) and the Division of Epidemiology I (DEPI), concluded that the product should not be approved due to this risk. DPP recommended the applicant conduct an active-controlled, parallel group study, with an active

control agent “which appears to have low risk for SIB events”, and frequently monitor trial subjects for psychiatric symptoms. The goal of such a trial would be “to further assess the suicide risk and determine if interventions such as psychological assessments could be useful in mitigation of any suicide risk associated with brodalumab.”

After reviewing the available data, the applicant concluded that a causal association with brodalumab use has not been established and pointed to several observations to substantiate their claim. First, they pointed out that an increased frequency of neuropsychiatric adverse events, such as depression and/or anxiety, which are known to be associated with SIB, was not observed and that SIB events were only observed in subjects with pre-existing psychiatric risk factors or documented psychosocial triggers. Further, they argued that prospectively evaluated depression and anxiety, in the one trial in which such data was collected, generally showed improvement from baseline over the course of that trial. They also point out design features of the trials that resulted in the majority of trial subjects receiving brodalumab, including those initially randomized to placebo or ustekinumab treatment; they postulated these design features could lead to an imbalance of observed events in subjects receiving brodalumab. Finally, they pointed out that their clinical development program, unlike other development programs for similar products, did not exclude subjects with history of depression and/or SIB from enrolling in the clinical trials.

Following extensive, multidisciplinary review of the data, Advisory Committee discussion, and internal discussions which included presentations at the Risk Evaluation and Mitigation Strategy (REMS) Oversight Committee, the CDTL concluded that brodalumab should be made available with labeling sufficient to describe and inform this risk as well as a REMS with Elements to Ensure Safe Use (ETASU); these measures will insure that prescribers understand and acknowledge the risks, and document that patients who use brodalumab are fully consented regarding the benefits and potential risks. Labeling will include a Boxed Warning about the risk of SIB; the indication will limit use of Siliq to patients who have failed to respond, or have lost response to other systemic therapies; labeling will contain a recommendation to reassess the need to continue therapy in patients who do not achieve an adequate response after 12-16 weeks. The ETASU will include one-time physician and pharmacy certification, and a patient-prescriber agreement form that must be signed prior to receipt of a prescription for brodalumab. The agreement form will document that the patient has received counseling about the potential risk of SIB, the importance of keeping the Siliq REMS Program wallet card with them at all times and the need to seek medical attention should they experience emergence or worsening of SIB.

I concur with the CDTL that brodalumab should be made available with sufficient product labeling and the proposed REMS with ETASU. Despite the availability of multiple alternatives for the treatment of psoriasis, none are universally effective for all patients and most severely affected patients generally lose response to the products they use over time. Additionally, a few patients may be uniquely responsive to certain classes of therapies or individual products and not to others. Siliq is clearly efficacious and this point is not in dispute; what is unknown is for how many psoriasis patients brodalumab will be the only treatment option. It is unclear if this information is important in the risk-benefit assessment; most of the other available psoriasis therapies have significant, potentially life-threatening risks associated with their use. I believe an important factor in the risk-benefit consideration that makes suicide uniquely concerning is the lack of opportunity on the part of the prescribing physician or other care providers to intervene once an event has occurred. The Siliq REMS will insure that prescribers understand and acknowledge this risk and document that patients who use brodalumab are fully consented regarding the benefits and potential risk of SIB. Patients will be provided with a wallet card that provides explicit advice to seek medical attention or to call the National Suicide Prevention Lifeline at 1(800) 273-TALK (8255) if they experience suicidal thoughts. Additionally, product labeling will limit the indication to those patients who have failed to respond, or lost response to other systemic therapies. This approach to risk mitigation is consistent with the message heard clearly at the Dermatologic and Ophthalmic Drugs Advisory Committee (DODAC) meeting held on July 19, 2016, that this product should be approved, that access should not be overly burdensome and that providers and patients must be made aware of the suicidality signal.

In weighing the risks and benefits of this product for psoriasis and the need to mitigate this risk, some suggested that current or past histories of depression and/or SIB should be a contraindication to Siliq use. Indeed, a concerning observation in this development program is that Siliq users with a history of suicidality had an approximately 12-18 fold increase in the incidence of suicidal ideation and behavior than users without such a history. Despite this observation, I find this approach to be problematic for two reasons. First, as observed in the one Phase 3 clinical trial in which depression and anxiety were prospectively assessed, more subjects who reported depression and anxiety at baseline reported improvement or resolution at Week 12 when treated with brodalumab as compared to placebo. While this evaluation has significant limitations, it is reasonable to conclude that most patients with depression and anxiety could expect to experience an improvement in these symptoms with brodalumab treatment. Second, this approach may have the unintended consequence of patients withholding important information about their medical history and mental state in order to receive or continue to receive brodalumab and may prevent them from fully engaging in their own medical care.

I disagree with any recommendation that another randomized, active-comparator clinical trial could successfully elucidate the risk of SIB associated with brodalumab use, and further, evaluate the impact of potential interventions. First, there is no product approved for psoriasis which could be reasonably concluded to have a low risk for SIB events; data on SIB in psoriasis clinical trials has never been prospectively collected using validated instruments (please refer to Division Director Opening Remarks in the July 19, 2016 DODAC meeting transcript). Even if it could be

concluded that a suitable comparator appeared to have a low risk for SIB, such a trial would be infeasible, given the rarity of the event (suicide attempts + completed suicides), sample size requirements, and the duration of follow-up required. An attempt to evaluate the impact of potential interventions would further increase the sample size requirements and complexity of trial design. I believe that even an attempt to answer these questions in a randomized, clinical trial is infeasible and imprudent, given the likelihood that such a trial would not provide convincing comparative risk estimates or be designed in such a way as to successfully evaluate any risk mitigation strategy.

Other ways to further assess the suicidality signal in the post-marketing setting were considered. 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. 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. A negative study would be unlikely to inform labeling.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	<p>Psoriasis is a common, chronic skin disorder affecting over 7 million patients in the United States. Plaque psoriasis is the most common variant and is generally characterized by well-demarcated erythematous plaques with silver scales. Patients with chronic plaque-type psoriasis usually present with symmetrically distributed cutaneous plaques. The scalp, extensor elbows, knees, and back are common sites for involvement. The extent of involvement can range from limited localized disease to involvement of the majority of the body surface area. Plaque psoriasis tends to be a chronic disease, but there may be marked variability in severity over time. About 1/3 patients with psoriasis also have psoriatic arthritis. About 1/5 patients have moderate to severe psoriasis that make them candidates for systemic therapies.</p> <p>From a patient perspective, psoriasis can be a debilitating chronic disease that places a significant burden on their daily lives and has a tremendous impact on how they feel and function. Psoriasis can place limitations on activities, career choices and intimacy, and create embarrassment, stigma and social discrimination. Scaling/flaking, itching, dry cracked skin, pain, burning, and stinging are among the most bothersome symptoms of psoriasis. Depression/anxiety, suicidality and obesity are more common in psoriasis patients than in the general population.</p>	<p>Psoriasis is a common, chronic skin disorder that in its moderate to severe manifestations can significantly impact how patients feel and function. It can place significant limitations on professional and personal activities and create embarrassment, stigma, social discrimination and isolation.</p> <p>Depression, anxiety and suicidality are more common in psoriasis patients than in the general population.</p>
Current Treatment Options	<p>There are many available topical therapies for patients with mild to moderate disease and ten approved systemic therapies for patients with moderate to severe disease. Available biologic products include the TNF blockers (etanercept, adalimumab, infliximab), an IL-12/23 blocker (ustekinumab), and the recently approved IL-17 blockers (secukinumab and ixekizumab). Available drug products include acitretin, methotrexate, cyclosporine and apremilast.</p> <p>All of the currently available therapies have potentially significant risks associated with their use. The risks generally associated with the use of biologic products include the risk of development of serious infections (including TB), malignancies and hematologic events such as neutropenia. Some are associated with a risk of demyelinating disease, leukoencephalopathy, hepatotoxicity or exacerbation of Crohn's disease. The risks associated with the use of drug products varies by</p>	<p>While there are at least ten systemic therapies currently approved for psoriasis treatment, none are universally effective and all of them are associated with potentially serious adverse effects. Patients must learn through trial and error which products will work for them and some patients will experience an eventual waning of efficacy with the ones that are initially effective.</p> <p>Additional efficacious products with favorable safety profiles are needed for psoriasis.</p>

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	<p>drug and includes teratogenicity, hepatotoxicity, liver fibrosis/cirrhosis, hematologic toxicity, interstitial pneumonitis, hypertension, nephrotoxicity, serious infections and depression</p> <p>The use of most systemic products can result in substantial improvement in psoriatic signs and symptoms, but the use of these products have significant limitations. Many patients with psoriasis on the more severe end of the spectrum tend to have unremitting disease requiring continuous treatment and many of those using systemic agents will experience an eventual waning of treatment effect over time. Few patients can remain on one therapy over the course of their disease.</p>	
Benefit	<p>To support an efficacy claim for Siliq for the treatment of psoriasis, the applicant submitted results from three Phase 3 randomized, double-blind, placebo-controlled clinical trials. All three trials included a placebo arm and two trials included an ustekinumab active comparator arm. Eligible subjects were patients with moderate to severe disease who were candidates for systemic or phototherapy.</p> <p>About 4300 subjects were enrolled in psoriasis trials. Baseline demographics were generally balanced across the treatment arms. About 70% of the subjects were male and 91% were Caucasians. The mean age was around 45 years and the mean weight was about 91 kg. The baseline median PASI was 17.4 with ranges of 12 to 72 and the median body surface area (BSA) was about 21 with ranges of 10 to 97. Approximately 58%, 37%, and 5% of the subjects had sPGA scores of 3 (moderate), 4 (severe) and 5 (very severe) at baseline, respectively. About 1/3 of enrolled subjects had received prior systemic biologic therapy.</p> <p>For all three pivotal trials, the protocol-specified co-primary endpoints for the comparison of each dose of brodalumab versus placebo were the proportion of subjects with sPGA of 0 or 1 and the proportion of subjects with PASI 75 at Week 12.</p> <p>The proportion of brodalumab-treated subjects achieving PASI 75 across the three trials was 85% and the proportion achieving sPGA of 0 or 1 was 79% as compared to 5% of placebo-treated subjects achieving PASI 75 and less than 5% achieving sPGA of 0 or 1. Similar results were obtained for PASI 75 response at Week 12 by subgroups of gender, age, race, weight, prior biologic use, and region. The majority of subjects enrolled were Caucasian and under the age of 65 years, so any differences for non-Caucasians and older subjects would be difficult to detect.</p> <p>Two of the Phase 3 trials included a re-randomized phase during which subjects originally randomized to receive Siliq during the first 12 weeks were re-randomized to one of four Siliq dose regimens at the Week 12 visit. For sPGA 0 or 1 responders at Week 12, the percentage of subjects who maintained this response (sPGA of 0 or 1) at Week 52 was 79% for subjects</p>	<p>Brodalumab was highly efficacious for the treatment of adults with moderate to severe plaque psoriasis in Phase 3 clinical trials.</p> <p>The major efficacy findings are:</p> <ol style="list-style-type: none"> 1) In three Phase 3 clinical trials, the proportions of patients treated with brodalumab 210 mg every 2 weeks who achieved a PASI 75 and an sPGA of 0 or 1 at Week 12 was significantly greater than placebo-treated subjects. 2) In one clinical trial, among responders at Week 12, significantly greater numbers of subjects re-randomized to continue brodalumab maintained treatment response as compared to subjects re-randomized to placebo. 3) In two Phase 3 clinical trials which included ustekinumab as a comparator, the numbers of subjects achieving PASI 75 and sPGA of 0 or 1 was numerically greater in the brodalumab group.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	<p>treated with the to-be-marketed dose of SILIQ 210 mg Q2W</p> <p>In one of the Phase 3 trials, subjects were re-randomized at Week 12 to continue their originally assigned Siliq dose or to receive placebo. At Week 52, 2% of subjects receiving placebo maintained their response (SPGA of 0 or 1)</p>	
Risk	<p>Across all psoriasis studies, 4145 subjects were exposed to brodalumab for ≥ 3 months, 3072 subjects were exposed for ≥ 12 months, 1220 subjects were exposed for ≥ 18 months, and 102 subjects had follow-up for over 5 years</p> <p>Adverse drug reactions (ADRs) that occurred with a $\geq 1\%$ overall incidence rate in the brodalumab group and that occurred more frequently than in the placebo group were headache, arthralgia, fatigue, oropharyngeal pain, influenza, diarrhea, nausea, myalgia, injection site reactions, neutropenia and tinea infections. ADRs identified through the sponsor's review through Week 12 across all psoriasis studies that occurred in $< 1\%$ of subjects in the Siliq group include conjunctivitis and candida infections. Adverse events that were reported as the reason for study discontinuation in more than one brodalumab-treated subject were neutropenia, arthralgias and urticaria (2 subjects each)</p> <p>The review identified the following serious risks:</p> <ul style="list-style-type: none"> • Suicide - Six completed suicides were reported during the conduct of the brodalumab development program, including four that occurred in the psoriasis clinical trials. The rate of suicide observed in this program is higher than expected when compared to other development programs enrolling similar populations. These types of crude cross-study comparisons are problematic and limited by a number of factors including heterogeneity in patient characteristics, follow-up methods and ascertainment of suicidal ideation and behavior (SIB) events. Additional uncertainty is introduced to the potential association of brodalumab use to the event of suicide because no increase was observed in other events that may lie on the causal pathway to suicide, which include depression, anxiety and other neuropsychiatric symptoms such as impulsivity. However, signals for such events may have been masked by a higher background incidence of depression and anxiety than is observed with brodalumab use coupled with the observation in the clinical trials that pre-existing depression and anxiety improved in most subjects when psoriasis was successfully treated. Finally, neuropsychiatric adverse events were underreported, as evidenced by a ten-fold increase in the incidence of suicidality following the implementation of prospective screening for depression and suicidality during the clinical trials. <p>Of particular concern is the observation in the extended open-label portion of the clinical</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 users with a history of suicidality or depression had an approximately 12-18 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 antidrug 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>trial that 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 or depression had an approximately 12-18 fold increase in the incidence of suicidal ideation and behavior than users without such a history</p> <p>The following other serious risks will be described in the Warnings and Precautions section of product labeling:</p> <ul style="list-style-type: none"> • Serious Infections - The Th17/interleukin (IL)-17 axis plays an important role in host defense against infectious pathogens and is particularly focused on immunity against extracellular pathogens and fungi. Observations in humans with genetic defects affecting the Th17 pathway and in individuals who have genetic defects in IL-17 signaling suggest that blockade of IL-17 increases the risk for fungal infections, particularly mucocutaneous candidiasis, as well as staphylococcal skin infections. In the psoriasis clinical trials, tinea and candida infections were identified as adverse drug reactions associated with brodalumab use; one event of candida esophagitis led to study discontinuation. Two subjects reported serious opportunistic infections; one event each of cryptococcal meningitis and coccidioidomycosis. Grade 4 serious infections were also reported; one event each of appendicitis, sepsis in the setting of suspected narcotic overdose, cholecystitis, furuncle and streptococcal necrotizing fasciitis complicated by sepsis. <p>If a patient develops a serious infection or if they are not responding to standard therapy for an infection, the product label recommends that brodalumab be discontinued until the infection resolves.</p> <ul style="list-style-type: none"> • Risk for Latent Tuberculosis Reactivation - Labeling will recommend that patients be evaluated for tuberculosis (TB) infection prior to initiating treatment with brodalumab. Patients with latent TB should initiate treatment prior to initiating brodalumab. Patients receiving brodalumab should be monitored for signs and symptoms of active TB during and after treatment. • Crohn's Disease - In psoriasis trials, which excluded subjects with active Crohn's disease, Crohn's disease occurred in one subject during treatment with brodalumab and led to discontinuation of therapy. In other trials for other indications that included subjects with Crohn's disease, exacerbation of Crohn's disease was observed with brodalumab use. Product labeling will reflect that brodalumab is contraindicated in patients with Crohn's disease and that brodalumab should be discontinued if the patient develops Crohn's disease while taking it. • Immunizations – Labeling will recommend avoiding the use of live vaccines in patients treated 	

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	with brodalumab No data are available on the ability of live or inactive vaccines to elicit an immune response in patients being treated with brodalumab	
Risk Management	1 SIB 2 Infections 3 Risk for Latent Tuberculosis Reactivation 4 Crohn's Disease 5 Immunizations 6 Neutropenia 7 Immunogenicity 8 CYP450 substrates 9 Potential for increased risk of malignancy	<p>Risk mitigation strategies include the following elements:</p> <p>Product labeling:</p> <ul style="list-style-type: none"> • A Boxed Warning describing the risk of suicidality observed with brodalumab • Indications and Usage will state that brodalumab should only be used in patients who have failed to respond, or have lost response, to other systemic therapies • Dosage and Administration will include a recommendation to discontinue brodalumab in patients who do not achieve an adequate response within 12-16 weeks • The W&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 This section will also include language about the risk of reactivation of latent TB, worsening of Crohn's disease, and unknown response to live or inactive vaccines in patients treated with Siliq • The Adverse Reactions section of labeling will describe the incidence of neutropenia and the development of anti-drug antibodies and neutralizing antibodies (NAb) observed in the clinical trials • The Drug Interactions section of labeling will make management recommendations for concomitant drugs which are CYP450 substrates upon initiation or discontinuation of Siliq • Section 13 of product labeling will convey the potential effect of brodalumab on malignancy risk, based on review of the published literature <p>A REMS with ETASU will be required The goal of the REMS will be to mitigate the potential risk of suicidal ideation and behavior by:</p>

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		<ul style="list-style-type: none"> • Ensuring that prescribers are educated about the potential risk of suicidal ideation and behavior observed with SILIQ therapy and the need to counsel patients about this risk • Ensuring that patients are informed about the potential risk of suicidal ideation and behavior observed with SILIQ therapy and the need to seek medical attention should they experience emergence or worsening of suicidal thoughts and behavior <p>Elements to Assure Safe Use:</p> <ul style="list-style-type: none"> • Healthcare providers who prescribe brodalumab must be certified. The certification is a one-time process that requires the HCP to enroll in the Siliq REMS program • Pharmacies that dispense Siliq must be certified. To become certified, an authorized pharmacy representative must submit an enrollment form on behalf of the pharmacy. The authorized representative must ensure that processes and procedures are put in place to ensure Siliq prescribers are enrolled in the REMS program before the pharmacy dispenses Siliq. • Patients must be enrolled in the Siliq REMS program. A patient-prescriber agreement form will document that the patient has received counseling about the potential risk of SIB, the importance of keeping the Siliq REMS Program wallet card with them at all times and the need to seek medical attention should they experience emergence or worsening of SIB. <p>ARIA will be used for surveillance of post-marketing occurrences of serious infections (broadly defined) and cases of hospitalized neutropenia.</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. Post-marketing data on the occurrence of opportunistic fungal and TB infections will be collected in the required observational study of malignancy.</p>

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		<p>The applicant will conduct enhanced pharmacovigilance (EPV) for the following Adverse Events of Special Interest:</p> <ul style="list-style-type: none"> • Suicidal Ideation and Behavior (SIB) • Cardiovascular Events/Major Adverse Cardiac Events (MACE) • Infections • Crohn's Disease • Neutropenia • Hypersensitivity • Malignancy

1. Background

Psoriasis is a common, chronic skin disorder affecting over 7.5 million patients in the United States. Plaque psoriasis is the most common variant of psoriasis and is generally characterized by well-demarcated erythematous plaques with silver scales. Patients with chronic plaque-type psoriasis usually present with symmetrically distributed cutaneous plaques. The scalp, extensor elbows, knees, and back are common sites for involvement. The extent of involvement can range from limited localized disease to involvement of the majority of the body surface area. Involvement of intertriginous areas (inverse psoriasis), the ear canal, umbilicus, palms, soles, or nails also may be present. Plaque psoriasis tends to be a chronic disease, but there may be marked variability in severity over time.

Psoriasis is likely a genetic disease with cycles of inflammation and cellular proliferation that typically result in clinical skin plaques. IL-17A is a naturally occurring cytokine that is involved in normal inflammatory and immune responses and also plays a role in the pathogenesis of plaque psoriasis. The subject of this application, Siliq (brodalumab), is a human monoclonal immunoglobulin G2 (IgG2) which binds to human interleukin-17 receptor A (IL-17RA) and blocks the biologic activities of IL-17A, IL-17C, IL-17F, IL-17A/F heterodimer and IL-25.

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

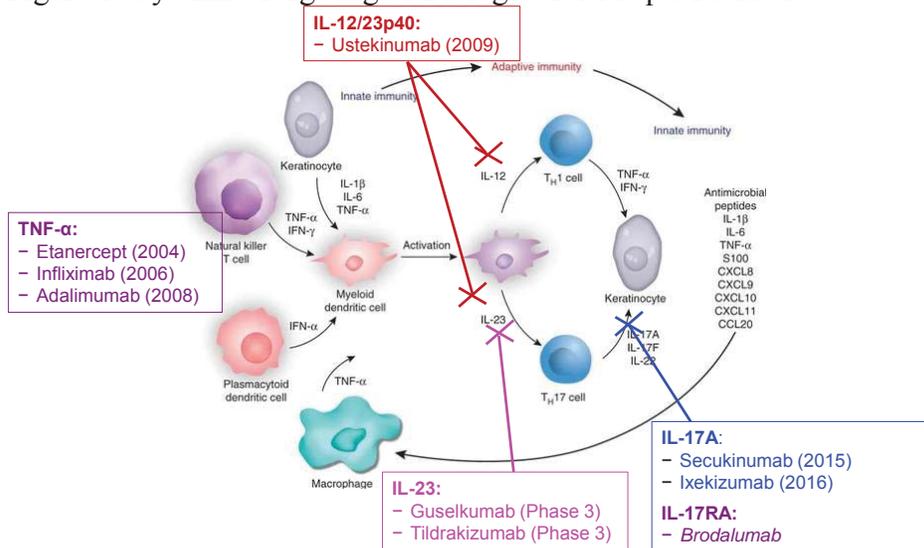
Currently available approved systemic treatments for moderate to severe psoriasis in candidates for systemic therapy or phototherapy are described in Table 1 below. While Siliq and two recently approved IL-17A antagonists (Cosentyx and Taltz) block the action of IL-17, other biologics both approved and under development target different cytokines in the inflammatory cascade (see Figure 1). Multiple topical therapies are also available and may be used in combination with systemic treatments, but topical therapies are not typically used alone for patients with psoriasis of moderate to severe severity.

Table 1: Approved Systemic Therapies for Psoriasis

Small Molecule Therapies			
Product	Year approved	Class	Warnings/Precautions
Acitretin	1996*	Retinoid	teratogen; hepatotoxicity; hyperostosis; lipid effects
Methotrexate	1953*	folate antagonist	teratogen; liver fibrosis/cirrhosis; hematologic toxicity; interstitial pneumonitis; opportunistic infections
Cyclosporine	1995*	inhibits IL-2	hypertension; nephrotoxicity; serious infections; malignancy
Apremilast	2014	Phosphodiesterase-4 inhibitor	depression; weight decrease; drug-drug interactions
Biologic Therapies			
Etanercept	2004	TNF α -blocker	serious infections (including TB); malignancy; central nervous system demyelinating disorders; hematologic events (pancytopenia); reactivation of hepatitis B; autoimmunity
Infliximab	2006	TNF α -blocker	serious infections (including TB); malignancy; demyelinating disease; hepatotoxicity
Adalimumab	2007	TNF α -blocker	serious infections (including TB); malignancy; reactivation of hepatitis B; demyelinating disease; hematologic reactions (pancytopenia); autoimmunity
Ustekinumab	2009	Interleukin-12 and -23 antagonist	serious infections; malignancy; reversible posterior leukoencephalopathy syndrome
Secukinumab	2015	Interleukin-17A antagonist	serious infections; TB, exacerbation of Crohn's, hypersensitivity
Ixekizumab	2016	Interleukin-17A antagonist	infection, hypersensitivity, exacerbation of Crohn's

Source: BLA 761032 brodalumab FDA briefing document for July 19, 2016 Advisory Committee

Figure 1: Cytokine Targeting of Biologics for Plaque Psoriasis



Source: BLA 761032 brodalumab FDA briefing document for July 19, 2016 Advisory Committee

The use of most systemic products can result in substantial improvement in psoriatic signs and symptoms, but the use of these products have significant limitations. Many patients with psoriasis on the more severe end of the spectrum tend to have unremitting disease requiring

continuous treatment and many of those using systemic agents will experience an eventual waning of treatment effect over time. Few patients can remain on one therapy over the course of their disease. Additionally, as described in Table 1, all systemic products currently available are associated with potentially serious risks.

The psoriasis development program for brodalumab included 12 studies in support of the indication; 7 Phase 1 PK/PD studies, 2 Phase 2 dose-ranging studies and 3 Phase 3 efficacy and safety trials. The Siliq development program also included additional data from clinical trials for other indications as well as product quality and pharmacology/toxicology data.

The product will be given by prefilled syringe (PFS) as a subcutaneous injection of 210 mg (140 mg/mL, 1.5 mL PFS) at 0, 1, and 2 weeks, with subsequent doses administered every two weeks (Q2W).

2. Product Quality

For complete details, please refer to Office of Product Quality's (OPQ) Integrated Quality Assessment completed by the Quality Review Team. From a product quality perspective, the application, as amended, is approvable.

Brodalumab is a human IgG2 monoclonal antibody produced in CHO ^{(b) (4)} cells ^{(b) (4)}. Brodalumab drug product is supplied at 210 mg/1.5mL as a sterile, single-dose, preservative-free solution for injection in a pre-filled syringe (PFS) containing a sterile, preservative-free clear to slightly opalescent, colorless to slightly yellow solution. Each sterile prefilled syringe contains 140 mg/mL brodalumab in 30 mM glutamate, 2.4% (w/v) proline, and 0.01% (w/v) polysorbate 20 filled to deliver a volume of 1.5 mL to provide 210 mg of brodalumab.

Initial review of the application resulted in multiple requests to the applicant for additional information about or revisions to drug substance and drug product specifications, reference standards, process characterization and validation, product quality monitoring/control and methods validation. The sponsor's responses to these issues were reviewed and found to be acceptable. The data submitted in this BLA support the conclusion that the manufacture of Siliq is well-controlled and leads to a product that is pure and potent. The product is free from endogenous and adventitious infectious agents sufficient to meet recommended parameters. The conditions used in manufacturing have been sufficiently validated, and a consistent product has been manufactured from the multiple production runs presented.

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.

3. Nonclinical Pharmacology/Toxicology

The nonclinical review by Carmen Booker, PhD concludes that brodalumab is approvable from a pharmacology/toxicology perspective.

In repeat dose toxicity studies in cynomolgus monkeys dosed with 0, 10, 25 or 90 mg/kg/dose SC brodalumab weekly for six months, mild skin changes and histopathology (MD and 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 for this study was determined to be 90 mg/kg/dose.

Three groups of 16-19 pregnant cynomolgus monkeys were administered weekly SC injections of brodalumab (0, 25, 90 mg/kg) from GD 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. Because a standard 2-year carcinogenicity study was determined not to be practical, the sponsor conducted a literature review to assess the carcinogenic potential of IL-17RA inhibition, but the literature was not definitive. The majority of the references suggest there is no increased carcinogenic potential from IL-17RA or IL-17 inhibition. Due to conflicting reports in the literature over the role of IL-17 and malignancy, the non-clinical reviewer recommended postmarketing surveillance of malignancy report frequency compared to background rates to provide a determination of potential cancer risk for brodalumab. Nonclinical studies to assess the carcinogenic potential of brodalumab are not recommended.

4. Clinical Pharmacology

Please refer to the review completed by Jie Wang, Ph.D., the clinical pharmacology reviewer and Dhananjay Marathe, Ph.D., the pharmacometrics reviewer. The review team considers this BLA approvable from a clinical pharmacology perspective.

Based on population PK modeling, the absolute bioavailability of brodalumab is estimated to be about 55% following SQ administration, the time to maximum serum concentration is about 3 days, and the serum level is expected to drop below the assay quantification limit about 63 days after discontinuation of the 210 mg brodalumab treatment regimen. Brodalumab exhibited non-linear PK with brodalumab exposures increasing in a greater than dose-proportional manner and the clearance decreasing with increasing dose. Of note, brodalumab clearance and the volume of distribution increases as body weight increases, making body weight a significant covariate of these parameters.

The applicant's proposed dosing regimen (210 mg at Weeks 0, 1, 2, followed by Q2W dosing) of Siliq for the treatment of psoriasis is supported by efficacy data from the three pivotal Phase 3 clinical trials. The Phase 3 trials evaluated two brodalumab dosing regimens: 140 mg and 210 mg administered at Weeks 0, 1, and 2 followed by Q2W dosing. Both brodalumab 210 mg Q2W and 140 mg Q2W achieved significantly higher response rates compared to placebo in each of the three Phase 3 trials. The brodalumab 210 mg Q2W also achieved significantly

higher response rates than 140 mg Q2W both in the initial 12-week treatment period and in the maintenance treatment period through 52 weeks.

Exposure-response for the Static Physician’s Global Assessment [sPGA (0,1)] Response at Week 12

The Week 12 efficacy data demonstrated an exposure-response (E-R) relationship, specifically between observed brodalumab trough concentrations at Week 12 and sPGA (0,1) response rates. The E-R relationship is demonstrated in Figure 2:

Figure 2: Exposure-response for achieving sPGA (0,1) and sPGA 0 at Week 12 by observed brodalumab trough concentrations (C_{trough})

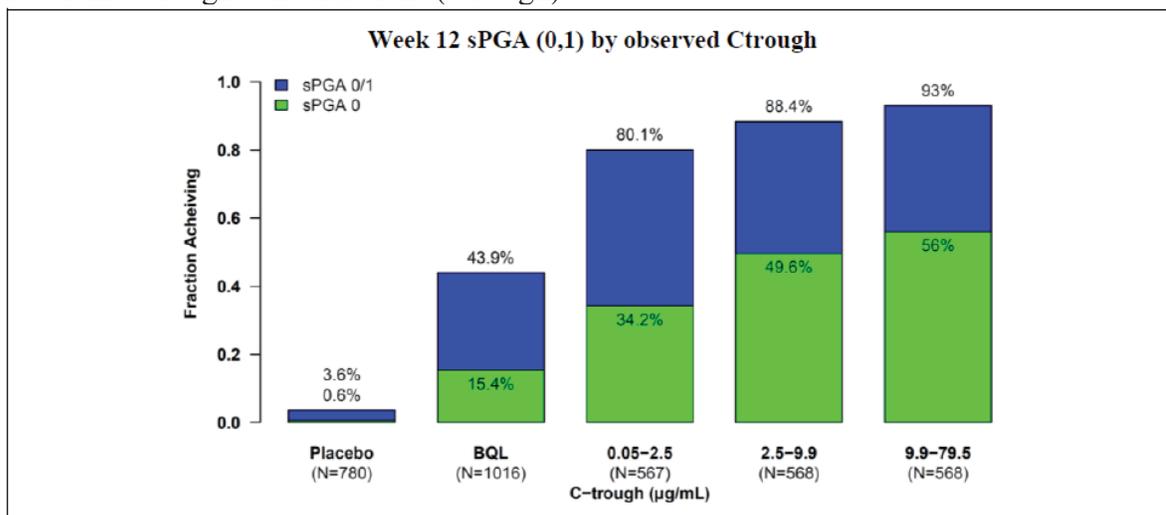


Figure 3.3.1.a. Exposure-response for achieving sPGA (0,1) and sPGA 0 at Week 12 by observed serum brodalumab trough concentrations (C_{trough}). (Data source: Figure 30, Summary of Clinical Pharmacology; Similar E-R relationships were found for between sPGA (0,1) and predicted AUC values, Appendix 2, Response to FDA IR, 02 February 2016)

As previously mentioned, body weight was identified as a significant covariate affecting brodalumab exposure in subjects with psoriasis and also showed an effect on efficacy. However, alternative dosing regimens adjusting for body weight is not recommended by the review team based on the following analysis results and considerations:

- For subjects with body weight >70 kg, the 210 mg dose consistently achieved greater PASI 75, PASI 90, PASI 100, sPGA (0,1) and sPGA (0) response rates at Week 12 than the 140 mg dose.
- For subjects with body weight ≤ 70 kg, the 210 mg dose achieved greater PASI 100 and sPGA (0) response rates at Week 12 than the 140 mg dose.
- The 210 mg dose achieved greater sPGA (0,1) response rates at Week 52 than the 140 mg dose in both body weight subgroups.
- Subgroup analyses using a body weight cutoff greater than 70 kg also favor the 210 mg dose in each body weight subgroup. The protocol predefined efficacy analyses using 100 kg as the cutoff support that 210 mg dose is superior to 140 mg dose.
- Reduction of the brodalumab dose to 140 mg in subjects with low body weight may not be associated with a lower risk for safety events.

The to-be-marketed presentation (a single 1.5 mL PFS) was demonstrated to be comparable to the Phase 3 presentations (1.5 mL dose delivered as a single 1.0 mL PFS and single 0.5 mL PFS) in a dedicated PK study. The results showed that the PK of the two presentations were within the acceptance limits of bioequivalence criteria.

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. Of the subjects who developed ADA, none (0%) were classified as positive for neutralizing antibodies. However, the incidence of development of neutralizing antibodies could be underestimated because the assay to test for neutralizing antibodies has limitations in detection in the presence of brodalumab. At Week 52, a trend of numerically lower sPGA response rates was observed in ADA positive subjects when compared to ADA negative subjects in Phase 3 trials.

In subjects with plaque psoriasis, one week following a single subcutaneous administration of 210 mg brodalumab, the exposure of midazolam (CYP3A4 substrate) was increased by 24% over baseline administration. One hypothesis to explain the increased midazolam exposure is that brodalumab treatment increased serum levels of cytokines which could inhibit the expression and/or activity of CYP enzymes.

5. Clinical Microbiology

Not applicable.

6. Clinical/Statistical-Efficacy

Please refer to the reviews completed by Carin Kim, Ph.D., the biostatistical reviewer, and Gary Chiang, M.D., the clinical reviewer for full details. Both reviewers find that the applicant has demonstrated the superiority of brodalumab to placebo when used by trial subjects with moderate to severe psoriasis who are candidates for phototherapy or systemic treatment.

To support an efficacy claim of Siliq for the treatment of psoriasis, the applicant submitted results from three Phase 3 clinical trials (Studies 20120102, 20120103, 20120104 from here on denoted as Trials 02, 03, and 04, respectively). All three trials included a placebo arm and Trials 03 and 04 included an ustekinumab active comparator arm. According to the applicant, ustekinumab was chosen as the active control in Trials 03 and 04 because it was the most efficacious treatment at the time of study design and was predicted to be the most commonly used treatment option at the time of approval. Ustekinumab was sourced from the U.S. and dosed according to the dosing recommendations provided in the U.S. and European Union labeling. To assess the effect of withdrawal and retreatment with Siliq, Trial 02 included a randomized withdrawal design following the 12-week induction period, and Trials 03 and 04 evaluated maintenance of efficacy from Week 12 through Week 52, followed by a long-term extension period. An overview of the trials is presented in Table 2.

Figure 3 presents the study design and treatment schema for Trial 02, and Figure 4 presents the study design schema for Trials 03 and 04. All Phase 3 trials were multicenter,

randomized, double-blind, placebo-controlled, parallel-group trials that included the following four phases:

- Screening: up to 30 days
- Induction : Day 1 to Week 12
- Randomized withdrawal (Trial 02) or maintenance (for Trials 03, and 04):
Week 13 to 52
- Long-term extension: Week 53 to up to 5 years

Table 2: Overview of Phase 3 Trials

	Trial 02	Trial 03	Trial 04
Study design	Multicenter, double-blind, randomized, placebo-controlled with induction, withdrawal, retreatment rescue, and open-label extension phases. Randomized withdrawal to assess the effect of withdrawal and retreatment with brodalumab.	Multicenter, double-blind, randomized, active-comparator and placebo-controlled with induction, withdrawal, retreatment rescue, and open-label extension phases	
Dates	8/29/2012-3/12/2014	8/22/2012-9/22/2014	9/11/2012-8/30/2014
Study Population	Men and women, 18-75 years of age with stable moderate and severe plaque psoriasis diagnosed at least 6 months before the first dose of investigational product, BSA \geq 10%, PASI \geq 12, sPGA \geq 3 at baseline. Subjects with prior psoriasis therapy, including biologic therapy, were allowed to participate; however, prior use of ustekinumab was prohibited in Trials 03 and 04.		
Number of Centers	73 centers in Europe (France, Germany, Poland, and Switzerland), Canada and U.S.	142 centers in Australia, Austria, Canada, Czech Republic, France, Hungary, Netherlands, Poland, Portugal, Spain and the U.S.	142 centers in Australia, Canada, Europe, and the U.S.
Number of subjects in the treatment arms	661 randomized in 1:1:1 ratio: <ul style="list-style-type: none"> • 222 Brodalumab 210 mg Q2W • 219 Brodalumab 140 mg Q2W • 220 Placebo 	1831 randomized in 2:2:1:1 ratio: <ul style="list-style-type: none"> • 612 Brodalumab 210 mg Q2W • 610 Brodalumab 140 mg Q2W • 309 Placebo • 300 Ustekinumab 	1881 randomized in 2:2:1:1 ratio: <ul style="list-style-type: none"> • 624 Brodalumab 210 mg Q2W • 629 Brodalumab 140 mg Q2W • 315 Placebo • 313 Ustekinumab
Randomization stratification	Randomization was done using the interactive voice response system (IVRS) that used permuted block design, and was stratified by baseline body weight (\leq 100 kg vs. $>$ 100 kg), by prior biologic use (yes vs. no), and by geographic region (non-U.S., US-West, US-Midwest, US-Northeast US-South).		

Source: Biometrics review by Dr. Carin Kim

Figure 3: Study Design for Trial 02

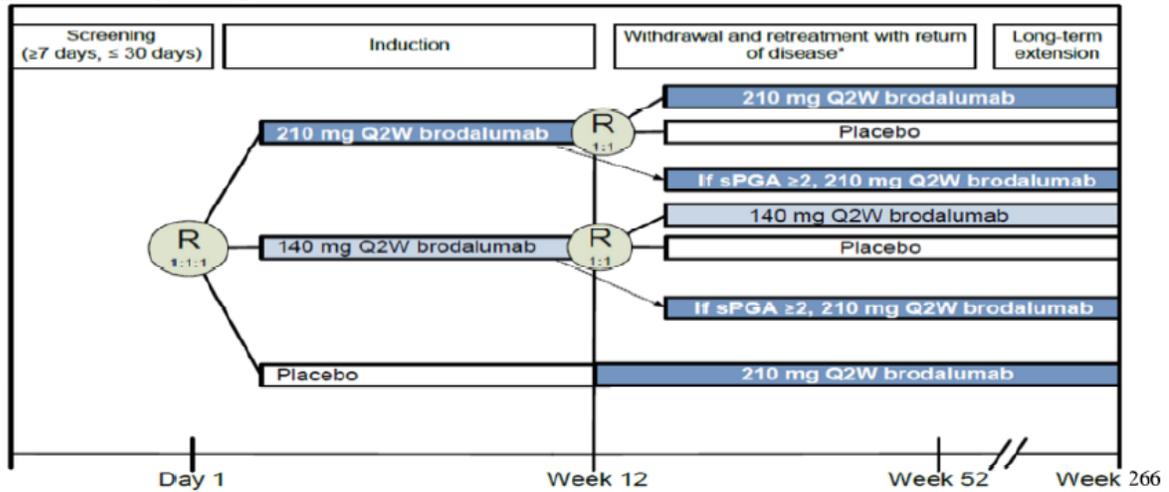
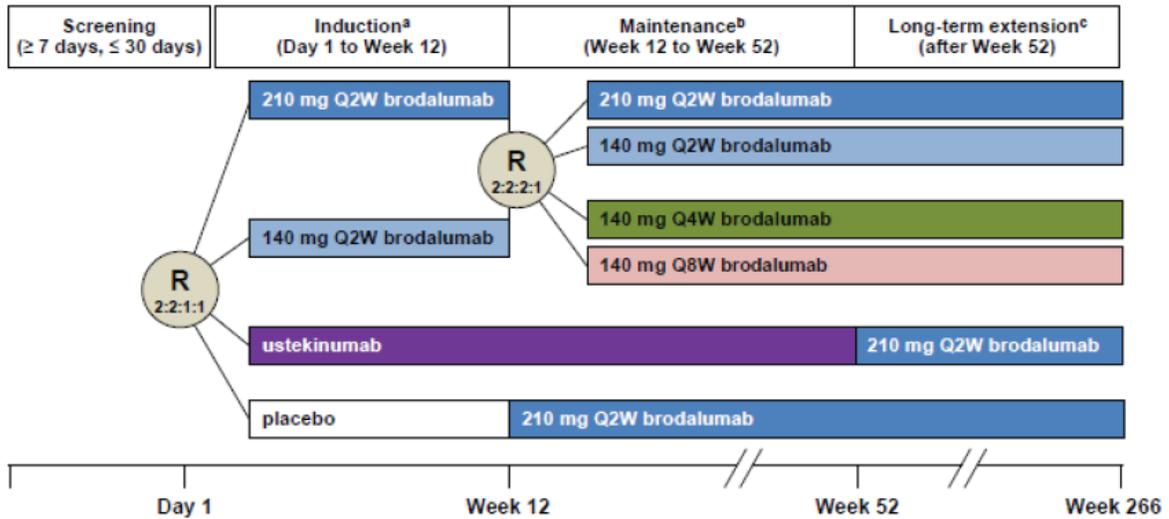


Figure 4: Study Design for Trials 03 and 04



Baseline demographics were generally balanced across the treatment arms within each trial; however, in Trial 02, history of prior biologic use was about 46% compared to 29% and 25% in Trials 03 and 04, respectively. About 69% of the subjects were male and 91% were Caucasians. The mean age was around 45 years and the mean weight was about 91 kg. About one-fourth of subjects weighed >100 kg. The baseline median PASI was 17.4 with ranges of 12 to 72 and the median body surface area (BSA) was about 21 with ranges of 10 to 97. Approximately 58%, 37%, and 5% of the subjects had sPGA scores of 3 (moderate), 4 (severe) and 5 (very severe) at baseline, respectively.

For all three pivotal trials, the protocol-specified co-primary endpoints for the comparison of each dose of brodalumab versus placebo were:

- The proportion of subjects with sPGA of 0 or 1 at Week 12

- The proportion of subjects with PASI 75 at Week 12,

and the secondary endpoints were:

- The proportion of subjects with PASI 100 at Week 12
- The proportion of subjects with sPGA of 0 at Week 12
- The proportion of subjects who were Psoriasis Symptom Inventory (PSI) responders defined as having a total score of ≤ 8 , with each item rated as either 0 (not at all) or 1 (mild) at Week 12.

Table 3 summarizes the efficacy results for the co-primary and key secondary endpoints for the Phase 3 trials,

Table 3: Proportion Achieving Treatment Success at Week 12 for Trials 02, 03 and 04

		Brodalumab 210 mg	Brodalumab 140 mg	Placebo	Ustekinumab	Weight- based ⁽¹⁾ 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 ⁽²⁾	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. >100 kg), prior biologic use (yes, no), geographic region, and baseline value of the endpoint (\leq median, $>$ median for PASI, 3, 4, 5 for sPGA).

Both brodalumab 210 mg and 140 mg were superior to placebo at Week 12 ($p < 0.0001$) for the co-primary endpoints of PASI 75 response and sPGA success (defined as scoring 0 or 1), 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 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). For the comparison of brodalumab 140 mg vs. ustekinumab, only Trial 04 was statistically significant (p -value=0.007) for the analysis of the

PASI 100 response at Week 12. The statistical reviewer noted a slightly higher mean baseline PASI score of 27 compared to the mean baseline PASI score of 20 for Trials 02 and 04.

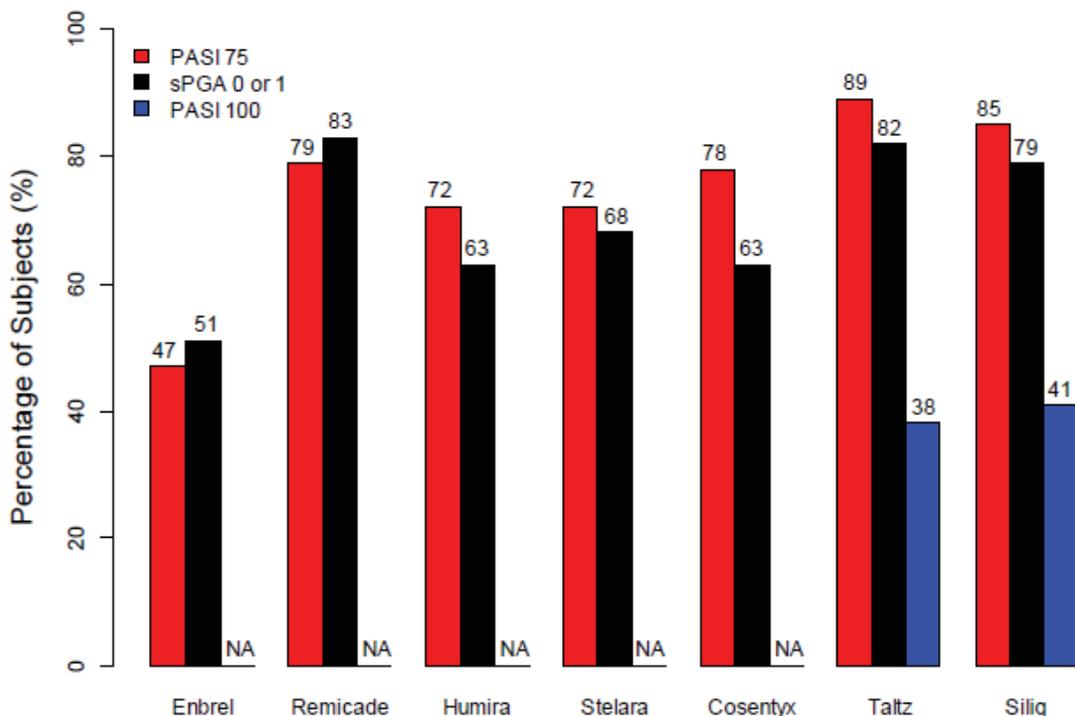
As represented in Figure 4, Trials 03 and 04 evaluated maintenance of sPGA success. As summarized in Table 4, at Week 52, the proportion of subjects who maintained their sPGA response was higher for subjects who received brodalumab 210 mg Q2W compared to brodalumab 140 mg doses (Q2W, Q4W, Q8W), and placebo. The proportion of sPGA responders that maintained their sPGA response status and received ustekinumab was higher than those subjects that received brodalumab 140 mg Q2W, but lower than those subjects that received brodalumab 210 mg Q2W.

Table 4: Maintenance of sPGA Response at Week 52 for Trails 03 and 04

Trial	Endpoint	Brodalumab 210 mg Q2W	Brodalumab 140 mg Q2W	Brodalumab 140 mg Q4W	Brodalumab 140 mg Q8W
03	sPGA 0 or 1	184/233 (79%)	134/234 (57%)	28/240 (12%)	7/123 (6%)
04	sPGA 0 or 1	190/242 (79%)	143/254 (56%)	48/244 (20%)	8/132 (6%)

Figure 5 shows efficacy results for the treatment of psoriasis from clinical trials conducted to support marketing applications for biologic products. This cross study comparison of efficacy was conducted by Dr. Carin Kim to help inform the risk-benefit analysis of brodalumab, in view of the suicides reported during the development program.

Figure 5: Efficacy Outcomes in Psoriasis Biologic Product Trials



Success defined as sPGA 0 or 1 was evaluated by gender, race, age, weight, prior biologic use, and region strata at baseline for the pivotal trials. The majority of the subjects enrolled in the

trials were Caucasians (approximately 91%), and of <65 years of age (approximately 94%). Therefore, any differences in efficacy for the non-Caucasians and the older age (≥ 65) 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.

7. Safety

The safety population for the review of this application includes 5205 subjects who received ≥ 1 dose of brodalumab in Phase 2 and 3 clinical trials. Data from psoriasis trials includes a total of 4461 subjects exposed to any dose of brodalumab through the data cutoff and represents a total of 5401.6 subjects-years of exposure. Across all psoriasis studies, 4145 subjects were exposed to brodalumab for ≥ 3 months, 3072 subjects were exposed for ≥ 12 months, 1220 subjects were exposed for ≥ 18 months, and 102 subjects had follow-up for over 5 years.

Adverse drug reactions (ADRs) that occurred with a $\geq 1\%$ overall incidence rate in the Siliq group and that occurred more frequently than in the placebo group were headache, arthralgia, fatigue, oropharyngeal pain, influenza, diarrhea, nausea, myalgia, injection site reactions, neutropenia and tinea infections. ADRs identified through the sponsor's review through Week 12 across all psoriasis studies that occurred in $< 1\%$ of subjects in the Siliq group include conjunctivitis and candida infections. Adverse events that were reported as the reason for study discontinuation in more than one brodalumab-treated subject were neutropenia, arthralgias and urticaria (2 subjects each).

Neutropenia has been recognized as an identified risk in association with administration of brodalumab. Interleukin-17A, IL-17F, and IL-17A/F play a role in the proliferation, maturation, and chemotaxis of neutrophils primarily via effects on granulocyte colony stimulating factor (G-CSF) production. A dose-dependent decrease in absolute neutrophil count (ANC) was observed in subjects with normal ANC at baseline (6.8% in the brodalumab 210 mg group, 4.7% in the brodalumab 140 mg group, 3.3% in the ustekinumab group, and 3.6% in the placebo group). Post-baseline ANC Grade 4 ($< 0.5 \times 10^9/L$) decreases were reported for 2 subjects in the 140 mg group and 1 subject in the ustekinumab group. None of the Grade 4 events were temporally associated with infections. Post-baseline ANC decreases of Grade 3 ($< 1.0 \times 10^9/L$ to $0.5 \times 10^9/L$) were reported for 10 brodalumab subjects (0.3%), including 7 subjects in the 210 mg group and 3 subjects in the 140 mg group, compared with none in placebo or ustekinumab subjects. Of these, 2 subjects in the 210 mg group and 2 subjects in the 140 mg group discontinued investigational product due to the event. Through the maintenance phase (52 weeks), the exposure-adjusted events rates (per 100 subject-years) for neutropenia were similar across all-brodalumab arm and ustekinumab arm.

The Th17/interleukin (IL)-17 axis plays an important role in host defense against infectious pathogens and is particularly focused on immunity against extracellular pathogens and fungi. Observations in humans with genetic defects affecting the Th17 pathway and in individuals who have genetic defects in IL-17 signaling suggest that blockade of IL-17 increases the risk for fungal infections, particularly mucocutaneous candidiasis, as well as staphylococcal skin

infections. As previously mentioned, tinea and candida infections were identified as ADRs associated with brodalumab use; one event of candida esophagitis led to study discontinuation. Two subjects reported serious opportunistic infections; one event each of cryptococcal meningitis and coccidioidomycosis. Grade 4 serious infections were reported only in subjects receiving brodalumab 210 mg; one case each of appendicitis, sepsis in the setting of suspected narcotic overdose, cholecystitis, furuncle and streptococcal necrotizing fasciitis complicated by sepsis.

Serious AE rates were low, with the highest incidences during the initial placebo-controlled, double-blind 12-week period from the Infections and Infestations system-organ class (SOC). The most frequently reported serious AEs by preferred term were cellulitis (0.1% brodalumab 210 mg Q2W, 0.1% brodalumab 140 mg Q2W, 0.2% ustekinumab), appendicitis (0.1% brodalumab 210 mg Q2W, 0.1% brodalumab 140 mg Q2W), acute pancreatitis (0.1% brodalumab 140 mg Q2W group, 0.1% placebo), and psoriasis (0.3% placebo). Serious AEs by preferred term with patient incidence rates $\geq 0.1\%$ in the all brodalumab group at Week 12 were cellulitis, appendicitis, gastroenteritis, and acute pancreatitis. Through Week 52, exposure adjusted rates of serious AEs were similar between the all-brodalumab group (8.3 per 100 subject-years) and the ustekinumab group (8.5 per 100 subject-years).

A total of 23 deaths were reported in subjects receiving brodalumab in clinical trials. Thirteen cardiovascular-related events included myocardial infarction (4), sudden death/cardiac arrest (3), cerebrovascular accident (2), and other single events (4). There were a total of 4 completed suicides, including one reported as an intentional overdose, 3 accidental deaths related to motor vehicle accidents and 3 other single unrelated fatal events. Major adverse cardiovascular events (MACE) and suicidal ideation and behavior (SIB) will be discussed separately in this review.

One of the primary safety concerns that emerged during the development program was suicidal ideation and behavior (SIB) and more specifically, the observed incidence of completed suicide. For the following discussion, suicidal ideation and behavior (SIB) events are defined as the following,

- Suicidal ideation
- Suicide behavior
- Suicide attempt
- Completed suicide

The first completed suicide in the brodalumab development program was reported to the Agency in March 2013. A cluster of suicide ideation and behavior events led the applicant to take the following actions in February 2014,

- Notify investigators of the potential safety issue through a Dear Investigator letter.
- Update the Investigator's brochure and informed consent with information about SIB events.
- Amend protocols with the following exclusion criteria,

- 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.

The eC-SSRS and PHQ-8 were incorporated into the clinical trials and administered at every visit to identify at-risk subjects (defined as subjects with suicidal ideation severity categories 4 or 5 or any suicidal behavior), who would then have investigational product permanently discontinued and would be immediately be referred to a mental health professional.

After meeting with the Agency on May 13, 2015 to discuss SIB events reported in the brodalumab development program, the current product sponsor, Amgen, announced on May 29, 2015, that they were no longer co-developing brodalumab and that they were terminating all ongoing clinical trials across all indications at that time.

In total, 6 completed suicides were reported in brodalumab clinical trials (4 in psoriasis, 1 in rheumatoid arthritis, and 1 in psoriatic arthritis); however, one suicide was later adjudicated as indeterminate due to possible accidental drug overdose. A comprehensive evaluation of SIB was undertaken by both the product sponsor and the Agency. The review of the SIB safety issue involved seven Divisions within the Center for Drug Evaluation and Research. Within the Office of New Drugs, the Division of Dermatology and Dental Products, the Division of Psychiatry Products and the Division of Biostatistics 7 conducted reviews of SIB safety data. Within the Office of Surveillance and Epidemiology, the Division of Epidemiology, the Division of Pharmacovigilance and the Division of Risk Management also conducted safety evaluations, as did the Division of Clinical Pharmacology 3 from the Office of Clinical Pharmacology. This memo attempts to highlight the main findings and conclusions from all of the reviewers.

The 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. The four suicide events occurred at times ranging from approximately 13 to 120 weeks after the subjects began their Siliq treatment and at 14 to 58 days after the subjects received their last 210 mg dose of Siliq. Based on available PK data, it appears unlikely that the suicidal events could be attributable to high brodalumab exposures either throughout the study or at the time of event. Table 5 provides selected demographic variables and other characteristics of all six subjects who completed suicide in the brodalumab development program.

Table 5: Patient Profiles for Completed Suicides

Trial	Age/Sex	Days from 1 st Dose	Days from Last Dose	History of Depression
PsO	56M	97	14	Y
PsO	39M	140	27	N
PsO	59M	329	58	N
PsO	56M	845	19	Y
PsA	57M	952	41	N
RA	42F	118	7	N

The safety database was comprised of data from the entire development program, which included studies conducted to evaluate the safety and efficacy of brodalumab for the treatment of psoriasis, psoriatic arthritis, rheumatoid arthritis, Crohn’s disease and asthma. In total, 44 of 6781 subjects in the safety database reported SIB. Among brodalumab users, 40 SIBs were identified, including 35 SIBs in PsO trials, 3 in the PsA trial and 2 in the RA trial.

Following implementation of the eC-SSRS and PHQ-8, 57 subjects were discontinued from clinical trials for positive scores: 43 subjects for positive PHQ-8 only, 8 subjects for positive eC-SSRS only and 6 subjects for positive PHQ-8 and eC-SSRS scores. The reasons listed for investigational product (IP) and study discontinuation were varied and included the following: protocol-specified criteria, ineligibility determined, administrative decision, lost to follow-up, consent withdrawn, non-response to investigational product, requirement for alternative therapy, adverse event and non-compliance.

The following analyses were conducted using data from the four active and/or placebo-controlled trials conducted for psoriasis: one Phase 2 trial, and three Phase 3 trials. Baseline demographics and selected baseline characteristics of this population are described in Table 6.

Table 6 - Baseline Demographics of the Psoriasis Safety Population

n (%)	Brodalumab n = 3066	Placebo n = 879	Ustekinumab n = 613
Male	2124 (69)	607 (69)	417 (68)
Age (years)			
Mean (SD)	44.8 (13)	44.6 (13)	45.1 (13)
< 40	1111 (36)	347 (39)	220 (36)
45-64	1763 (58)	476 (54)	351 (57)
>= 65	192 (6)	56 (6)	42 (7)
Country (US)	1335 (44)	381 (43)	280 (46)
Previous biologic usage	874 (29)	266 (30)	160 (26)
Psoriatic Arthritis	654 (21)	180 (21)	114 (19)
Psychiatric disorders	538 (18)	150 (17)	121 (20)
Depression*	430 (14)	117 (13)	98 (16)
Suicidality			
Yes	81 (3)	18 (2)	26 (4)
Unknown	409 (13)	90 (10)	80 (13)
No	2576 (84)	771 (88)	507 (83)

*Incidence of depression was calculated by the applicant using self-reported history or current use of anti-depressant medication

Source: DB7 review

Neuropsychiatric Adverse Events in the Psoriasis Clinical Trials

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 were analyzed to look for a pattern of adverse events that might indicate a risk for SIB. Of note, the brodalumab psoriasis studies did not exclude patients with a history of psychiatric disorders or substance use disorders. Ascertainment of the presence of such disorders was based on subject report; there were no formal diagnostic psychiatric assessments. In the controlled phases of these clinical trials, few psychiatric adverse events were reported and are summarized in Table 7.

Table 7: Neuropsychiatric Adverse Events in Active and/or Placebo-Controlled Psoriasis Clinical Trials

Adverse Event	PLACEBO N=879	BROD All Doses N = 3066	B 70mg Q2W N= 38	B 140mg Q2W n=1491	B 210mg Q2W N=1496	B 280mg Q4W N=41	UST N=613
Depression	5 (2.6)	14 (2)	0	9 (2.7)	5 (1.5)	0	3 (2.2)
Depressed mood	1 (0.5)	3 (0.4)	0	2 (0.6)	1 (0.3)	0	2 (1.4)
Anhedonia	0	0	0	0	0	0	1 (0.7)
Anxiety	2 (1)	13 (1.9)	0	10 (3)	3 (0.9)	0	3 (2.2)
Panic attack	0	1 (0.1)	0	0	1 (0.3)	0	0
Claustrophobia	1 (0.5)	0	0	0	0	0	0
Stress	1 (0.5)	3 (0.4)	0	0	3 (0.9)	0	0
Mood swings	0	3 (0.4)	0	1 (0.3)	2 (0.6)	0	0
Bipolar disorder	1 (0.5)	1 (0.1)	0	1 (0.3)	0	0	0
Suicide attempt	0	2 (0.3)	0	0	2 (0.6)	0	0
Emotional disorder	1 0.5	0	0	0	0	0	0
Confusional state	0	1 (0.1)	0	0	1 (0.3)	0	0
Insomnia	6 (3.1)	18 (2.6)	0	7 (2.1)	11 (3.3)	0	4 (2.9)
Insomnia, initial	0	1 (0.1)	0	1 (0.3)	0	0	0
Sleep disorder	0	1 (0.1)	0	0	1 (0.3)	0	0
Irritability	0	1 (0.1)	0	0	1 (0.3)	0	0
Libido increased	0	1 (0.1)	0	1 (0.3)	0	0	0
Apathy	1 (0.5)	0	0	0	0	0	0
Hallucination, olfactory	0	1 (0.1)	0	1 (0.3)	0	0	0

One of the controlled Phase 3 psoriasis trials, Study 02, included a systematic, prospective assessment of depression and anxiety symptoms at Baseline and Week 12. This was performed using the Hospital Anxiety-Depression Scale (HADS). The sponsor performed an analysis in the subset of subjects who exhibited moderate or severe symptoms at the study baseline assessment. As summarized in Table 8 below, subjects in the brodalumab group had higher degrees of improvement in depression and anxiety symptoms compared to the placebo group at Week 12.

Table 8: Change in HADS Score in Study 02 in Subjects with Baseline Moderate-Severe HADS Scores

Week 12 shift n (%)	Placebo	BROD 140 mg Q2w	BROD 210 mg Q2w
Depression	22	30	30
Improved	10 (45.5)	23 (76.7)	22 (73.3)
Improved to Normal	2 (9.1)	14 (46.7)	13 (43.3)
Remained the same	8 (36.4)	2 (6.7)	4 (13.3)
Worsened	3 (13.6)	1 (3.3)	1 (3.3)
Anxiety	27	37	42
Improved	8 (29.6)	25 (67.6)	28 (66.7)
Improved to Normal	2 (7.4)	12 (32.4)	18 (42.9)
Remained the same	11 (40.7)	5 (13.5)	10 (23.8)
Worsened	6 (22.2)	3 (8.1)	2 (4.8)

Source: DPV reviewer analysis of submitted data

Suicide Ideation and Behavior (SIB) During the Controlled Phases of the Psoriasis Clinical Trials

During the controlled 12-week induction phase, 1 subject experienced an SIB event in the brodalumab arm (n = 3066) and none in the comparator arms (placebo: n = 879; ustekinumab: n = 613). Note that the exposure time in this phase was not long enough to observe events or compare incidence of SIB among brodalumab and the placebo or ustekinumab comparator arms.

At the end of the 12-week induction period, the majority of placebo subjects and some ustekinumab subjects received brodalumab. During the 52-week active-controlled phase, seven SIB events occurred in the brodalumab arm, and three SIB events in the ustekinumab arm. The incidence of SIB among subjects exposed to brodalumab (including subjects who switched to brodalumab after receiving ustekinumab) was 0.17% (95% CI: 0.07–0.36), and the follow-up time adjusted incidence rate was 0.20 events per 100 subject-years (95% CI: 0.08–0.41). This data is summarized in Table 9.

Table 9: Number (%) and follow-up time adjusted incidence rates of SIB events during the active-controlled phase (first 52 weeks) of PsO trials

SIB	Brodalumab n = 3902	Brod after Ustek n = 124	Ustekinumab n = 613	Placebo n = 43
Number (%)	7 (0.18)	0	3 (0.49)	0
Follow-up time	3472.5	80.4	504.1	0
Incidence rate*	0.2	0	0.6	0
Brodalumab + Brodalumab after Ustekinumab n = 4026				
Number (%; 95% CI)	7 (0.17; 0.07–0.36)			
Follow-up time	3552.9			
Incidence rate* (95% CI)	0.2 (0.08–0.41)			

*per 100 subjects years

Source: DB7 Reviewer’s analysis

A subgroup analysis was conducted to estimate the incidence rate of SIB events among brodalumab users by the baseline depression status and suicidality status. Baseline depression was determined by reported medical history of depression and usage of antidepressants. A suicidality assessment was implemented following the initiation of the Phase 3 psoriasis trials through incorporation of the eC-SSRS. The eC-SSRS included assessment of baseline, lifetime history and since the study start SIB.

These analyses demonstrated that Siliq users with a history of depression had an approximately 7-fold increase in SIB incidence rate than users without a history. Siliq users with a history of suicidality had about a 12–18 fold increase in SIB incidence rate than users without a history.

The eC-SSRS was instituted when most subjects had reached at least Week 40 in the Phase 3 clinical trials. Despite the limitations of this assessment, worst on-study eC-SSRS responses were evaluated in the two active-comparator clinical trials and are summarized in Table 10.

Table 10: Proportion eC-SSRS response through Week 52 -MA Data Cutoff - Integrated Safety Analysis Set - Psoriasis Subset

Subgroup Events during treatment	Constant Dose				
	Ustekinumab n (%)	Brodalumab		All Brodalumab n (%)	All Subjects n (%)
		140 mg Q2W n (%)	210 mg Q2W n (%)		
All subjects	114	26	79	520	795
Any suicidal ideation or behavior (≥ 1)	3 (2.6)	2 (7.7)	5 (6.3)	23 (4.4)	32 (4.0)
Suicidal ideation (1-5)	3 (2.6)	2 (7.7)	5 (6.3)	22 (4.2)	30 (3.8)
Suicidal ideation with intent to act only (4-5)	1 (0.9)	0 (0.0)	0 (0.0)	1 (0.2)	2 (0.3)
Suicidal behavior only	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	2 (0.3)
Suicidal ideation (4-5) or behavior	1 (0.9)	0 (0.0)	1 (1.3)	3 (0.6)	5 (0.6)
With no prior suicidality history	104	25	74	497	754
Any suicidal ideation or behavior (≥ 1)	1 (1.0)	2 (8.0)	3 (4.1)	16 (3.2)	21 (2.8)
Suicidal ideation (1-5)	1 (1.0)	2 (8.0)	3 (4.1)	16 (3.2)	21 (2.8)
Suicidal ideation with intent to act only (4-5)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Suicidal behavior only	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Suicidal ideation (4-5) or behavior	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
With prior suicidality history	9	0	3	17	34
Any suicidal ideation or behavior (≥ 1)	1 (11.1)	0 (0.0)	0 (0.0)	3 (17.6)	6 (17.6)
Suicidal ideation (1-5)	1 (11.1)	0 (0.0)	0 (0.0)	3 (17.6)	5 (14.7)
Suicidal ideation with intent to act only (4-5)	0 (0.0)	0 (0.0)	0 (0.0)	1 (5.9)	1 (2.9)
Suicidal behavior only	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.9)
Suicidal ideation (4-5) or behavior	0 (0.0)	0 (0.0)	0 (0.0)	1 (5.9)	2 (5.9)
Unknown prior suicidality history	1	1	2	6	7
Any suicidal ideation or behavior (≥ 1)	1 (100.0)	0 (0.0)	2 (100.0)	4 (66.7)	5 (71.4)
Suicidal ideation (1-5)	1 (100.0)	0 (0.0)	2 (100.0)	3 (50.0)	4 (57.1)
Suicidal ideation with intent to act only (4-5)	1 (100.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (14.3)
Suicidal behavior only	0 (0.0)	0 (0.0)	0 (0.0)	1 (16.7)	1 (14.3)
Suicidal ideation (4-5) or behavior	1 (100.0)	0 (0.0)	1 (50.0)	2 (33.3)	3 (42.9)

On-study responses include "since study start", "since last contact", and recency responses since study start
N=subjects in Studies 20120103 & 20120104 with ≥ 1 dose of investigational product and ≥ 1 on-study eC-SSRS assessment through week 52.

Source: Sponsor's Table 30 in Summary of Clinical Safety Appendix 1.

The Division of Epidemiology I (DEPI-I) compared data on SIB in brodalumab clinical trials to data on SIB events observed in development programs for other psoriasis biologics. To do so, available data on suicides, suicide attempts, and suicidal ideation in clinical trials were extracted from submissions of recent psoriasis products. This analysis has important limitations which include,

- The analysis represents a crude pooling of data across product trials. It is not a patient or trial level meta-analysis.
- Heterogeneity in patient characteristics, follow-up methods and ascertainment of SIB cannot be fully evaluated.
- The clinical development programs for included products were conducted over different time periods, when national suicide rates appear to be different.
- C-CASA adjudication of SIB events was only conducted on datasets from four of the clinical programs: apremilast, secukinumab, ixekinumab and brodalumab.
- eC-SSRS retrospective and prospective assessment for SIB was only conducted during the brodalumab clinical development program. Ascertainment of suicidal ideation appeared to increase 10-fold following implementation of eC-SSRS.

Table 11 compares rates of completed suicides, attempted suicides, the combination of completed and attempted suicides, and suicidal ideation across development programs.

Table 11: Rates of Suicidal Ideation and Behavior (SIB) with Psoriasis Products

Rates of Suicidal Ideation & Behavior (SIB) with Psoriasis Products									
Dataset, indication	N	Exposure Patient - years	Completed suicides, N	Suicide Behaviors/ Attempts N	Suicides/ 100,000 PY	Attempts/ 100,000 PY	Suicides+ Attempts/ 100,000 PY	Suicidal Ideation, N	Ideation/ 100,000 PY
Brodalumab, all (updated from 120d SU)	6,243	10,438	6**	12 [§]	57.5	115.0 [§]	172.5 [§]	24 [§]	229.9 [§]
Brodalumab, Ps trials (from 120d SU)	4,464	9162	4**	11 [§]	43.7	120.1 [§]	163.7 [§]	22 [§]	240.1 [§]
Adalimumab, Ps	1,468	4,069	1**	0	24.6	0	24.6	3	73.7
Apremilast, Ps, PsA, RA‡	2,401	1,483	0 [†]	2	0	134.9	134.9	2	134.9
Etanercept, Ps	1,807	2,773	0	1	0	36.1	36.1	2	72.1
Infliximab, Ps	1,564	1,263	0	3	0	237.5	237.5	0	0
Ixekizumab, Ps	4,209	6,480	0	10	0	154.3	154.3	0	0
Secukinumab Ps, PsA‡	3,928	3,225	0*	1	0	31	31	1	31
Unapproved biologic, Ps	2,520	3,011	2**	0	66.4	0	66.4	1	33.2
Ustekinumab, Ps	3,117	6,791	1	0	14.7	0	14.7	0	0
Pooled w/o brodalumab, apremilast	18,613	27,612	4	14	14.5	50.7	65.2	7	25.4

*There was 1 suicide during screening for a Ps trial, and 1 suicide in an ankylosing spondylitis trial (treatment blinded)
 **Includes suicides during post-treatment follow-up †2 suicides occurred on placebo ‡Adjudicated with C-CASA
 §Includes events detected with the electronic Columbia Suicide Severity Rating Scale
 PY patient-years, Ps psoriasis, PsA psoriatic arthritis, RA rheumatoid arthritis, 120d SU 120 day Safety Update

Source: *Errata* to FDA background document for the July 19, 2016 DODAC meeting

An additional analysis was conducted by DEPI to compare pooled rates of completed suicides across other development programs to those observed in the brodalumab program and is summarized in Table 12. The applicant obtained an external consultant, Exponent, Inc., to prepare a systematic review of psoriasis biologics trials, using publicly available sources. This rate, as well as the rate obtained in DEPI's similar analysis of internal data sources are compared to the suicide rate in brodalumab trials. The rate observed in the brodalumab development program was 3-4 times higher than in pooled trials of other biologics for psoriasis. The proportion of all deaths that were due to suicide in brodalumab clinical trials (19%) was roughly twice the proportion in psoriasis trials of other biologics (9%), using the Exponent, Inc. analysis. In the same comparison, brodalumab was associated with a 3-fold higher than expected suicide rate (58 suicides/100,000 patient years vs 19 suicides/100,000 patient years).

Table 12 – Cross-study Comparative Analyses of Completed Suicides

Dataset	N	Exposure Patient - years	Completed suicides, N	Suicides/100,000 Patient-Years (95% CI)
Brodalumab, all trials	6,243	10,438	6	58 (21-125)
Brodalumab, psoriasis trials	4,464	9162	4	44 (12-112)
DEPI-I review of other psoriasis biologics submissions*	18,613	27,612	4	14 (4-37)
Amgen's systematic review of psoriasis biologics, Phase 3-4 trials	n/a	21,062	4	19 (5-49)

*A publication by the manufacturer of ustekinumab reported an additional 2,207 patient-years of exposure with 1 additional suicide, which, if added to the totals from the submissions, gives a rate of 17 per 100,000 patient-years (95% CI 5-39).

Source: DEPI review

Major Adverse Cardiovascular Events

MACE is defined as CV death, myocardial infarction, or stroke. A cardiovascular events committee (CEC) from Duke Clinical Research institute was formed to prospectively adjudicate MACE events in a blinded fashion in order to reduce investigator bias. The system organ classes (SOC) with the most deaths among brodalumab subjects were the Cardiac Disorders and the General Disorders and Administration Site conditions SOCs. The analysis for MACE only included the three Phase 3 clinical trials in psoriasis as MACE was only adjudicated for the Phase 3 clinical trials by a Cardiovascular Events Committee (CEC); therefore the Phase 2 trials were not included in these analyses.

During the induction phase, 3 (0.1%) MACE (2 MIs, 1 stroke) occurred in the brodalumab arm (n = 2908) and 1 (0.12%) MACE (MI) in the placebo arm (n = 842). MACE was not observed in the ustekinumab arm (n = 613).

At the end of the 12-week induction phase, the majority of placebo subjects and some ustekinumab subjects received brodalumab. During the active-controlled phase, 22 MACE events occurred in the brodalumab arm, and 1 MI was detected in the ustekinumab arm. The incidence of MACE among subjects exposed to brodalumab was 0.6% (95%CI: 0.38–0.90), and the follow-up time adjusted rates was 0.7 cases per 100 subject-years (95% CI: 0.4–0.9).

During the active-controlled phase, 22 MACE events occurred in the brodalumab subjects, and 1 MI occurred in the ustekinumab subjects. The incidence of MACE among subjects exposed to brodalumab was 0.6% (95%CI: 0.38–0.90), and the follow-up time adjusted rates was 0.7 cases per 100 subject-years (95% CI: 0.4–0.9).

The Division of Cardiovascular and Renal Products (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.”

8. Advisory Committee Meeting

The Dermatologic and Ophthalmic Drugs Advisory Committee of the Food and Drug Administration, Center for Drug Evaluation and Research, met on July 19, 2016, at the FDA White Oak Campus to discuss the Siliq application. Discussions and questions focused on the risk of SIB and MACE events with Siliq use.

The committee unanimously agreed that there was no safety signal for 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 had differing opinions about requiring a registry to follow patients taking brodalumab. The committee discussed the difficulty in evaluating patients for increased suicide risk unless a clinician had expert psychiatric experience. The committee also debated as to whether or not the proposed enhanced safety communications are adequate to address the issue of six completed suicides.

The voting question related to the risk/benefit assessment was as follows:

VOTE: 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.

Vote Result: A – 4 votes B – 14 votes C – 0 votes

Committee Discussion: The committee was unanimous in voting that the overall benefit/risk profile of brodalumab is acceptable to support approval for the treatment of moderate to severe plaque psoriasis in adult patients who are candidates for systemic therapy or phototherapy. They acknowledged that Siliq is efficacious and a need still exists for more effective therapies.

A majority considered that Siliq should be approved only if certain risk management options for SIB beyond labeling are implemented (Response B). Of those who voted for “B”, the majority stated that they supported a registry of some type, although they also acknowledged that additional barriers to access should not be the consequence of such measures. One committee member cautioned against a mandatory registry, stating that there are relatively few dermatologists in the U.S., about 8000, from which only a subset will be willing to participate. Another committee member cautioned that a voluntary registry won’t be able to answer the question about SIB due to inherent biases in patient selection for registry enrollment. A few

committee members stated their opinion that excluding patients with a history of depression and/or SIB may stop patients from disclosing their medical history in order to receive Siliq. Four committee members recommended a black box warning.

9. Pediatrics

Psoriasis vulgaris occurs in both children and adults, and although the disease prevalence varies with age, the pathophysiology is understood to be the same across all ages.

Additionally, there are no known age-related factors that would make the disease either more or less responsive to treatment in pediatric patients. Therefore, it is scientifically appropriate to extrapolate efficacy from the adult population to the pediatric population. None-the-less, appropriate doses for pediatric patients with acceptable safety and activity profiles will need to be defined and evaluated in clinical trials for the pediatric age group (b) (4) to <18 years of age. Studies in children less than (b) (4) years of age are considered to be highly impractical or impossible due to the very low incidence of psoriasis in this age group.

The applicant has proposed to conduct three pediatric studies in subjects with psoriasis:

- A single dose open-label PK study in 16 children ((b) (4) < 18 years old) with severe plaque psoriasis
- A double-blind active comparator-controlled, multicenter study to determine the safety and efficacy of brodalumab in adolescent subjects (12-<18 years old) with severe plaque psoriasis.
- An open-label, single arm study with brodalumab to determine the safety and efficacy in children (b) (4) to < 12 years) with severe plaque psoriasis.

On July 6, 2016, the PeRC met to discuss the SIB safety concerns identified in the review. They acknowledged the 6 completed suicides reported in the development program and agreed that studies should not be initiated in pediatric patients until the suicidality concern is clarified. The deferral for ages (b) (4)-17 is recommended until adequate adult, post-marketing data is sufficient for evaluation of SIB risk.

10. Other Relevant Regulatory Issues

The clinical sites of three trial investigators, Drs. Elzakowska-Bober, Lebwohl, and Toth, were inspected in support of this BLA, and the final classification of these inspections was No Action Indicated (NAI). Based on the results of the clinical investigator inspections, the studies appear to have been conducted adequately, and the data generated by these sites appear acceptable in support of the respective indication.

No issues related to Good Clinical Practice (GCP), financial disclosures, or patents were identified.

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.

11. Labeling

The following summarizes important labeling revisions required in order to ensure a favorable risk-benefit assessment of Siliq.

- Because of the six completed suicides observed in the brodalumab development program, a Boxed Warning will be required to describe the risk of suicidality observed with brodalumab.
- Indications and Usage will state that brodalumab should only be used in patients who have failed to respond, or have lost response, to other systemic therapies.
- Dosage and Administration will include a recommendation to discontinue brodalumab in patients who do not achieve an adequate response within 12-16 weeks.
- The W&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. This section will also include language about the risk of reactivation of latent TB, worsening of Crohn's disease, and unknown response to live or inactive vaccines in patients treated with Siliq.
- The Adverse Reactions section of labeling will describe the incidence of neutropenia and the development of anti-drug antibodies and neutralizing antibodies (NAb) observed in the clinical trials.
- The Drug Interactions section of labeling will make management recommendations for concomitant drugs which are CYP450 substrates upon initiation or discontinuation of Siliq.
- Section 13 of product labeling will convey the potential effect of brodalumab on malignancy risk, based on review of the published literature.

12. Postmarketing Recommendations

- Postmarketing Risk Evaluation and Mitigation Strategies

Title IX, Subtitle A, Section 505-1 gives the Secretary the authority, in consultation with the office responsible for reviewing the drug and the office responsible for post-approval safety with respect to the drug, to determine that a Risk Evaluation and Mitigation Strategy (REMS) is necessary to ensure that the benefits of a drug outweigh the risks of the drug.

On May 25, 2016 and again on August 9, 2016, the risk of SIB observed with brodalumab was discussed at REMS Oversight Committee meetings. The ROC recommended that a REMS with ETASU was necessary for the approval of brodalumab, in order to ensure the benefits outweigh its risks.

The goal of the Siliq REMS is to mitigate the potential risk of suicidal ideation and behavior (SIB) associated with Siliq by:

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

The Elements to Ensure Safe Use of Siliq include the following,

- Prescriber enrollment (A)
- Pharmacy enrollment (B)
- Documentation of safe-use conditions (D)

The Siliq REMS program materials will include the following,

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

A REMS supporting document which contains the goals of the REMS and the plan for assessment of the REMS was provided.

- **Postmarketing Requirements and Commitments**

Postmarketing Requirements under PREA:

- 1) Open-label study to determine PK of a single dose of brodalumab in 16 children ((b)(4) to < 18 years old) with severe plaque psoriasis.

Final protocol submission	06/01/2017
Trial completion	01/31/2019
Final report submission	06/31/2019

- 2) 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.

Final protocol submission	04/30/2019
Trial completion	01/31/2024
Final report submission	06/31/2024

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

Final protocol submission 04/30/2024
Trial completion 01/31/2029
Final report submission 06/31/2029

Postmarketing Requirements under Section 505(o):

- 4) 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.

Final protocol submission 12/01/2017
Trial completion 12/01/2022
Final report submission 06/01/2023

- 5) 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.

Final protocol submission 12/01/2017
Trial completion 06/01/2030
Final report submission 06/01/2031

- 6) Conduct a prospective, observational study to assess the long-term safety of 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, serious infection, tuberculosis, opportunistic infections, (b) (4).

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), clearly define the study

drug initiation period and any exclusion and inclusion criteria. Enroll patients over an initial 4-year period and follow for a minimum of 8 years from the time of enrollment.

Final protocol submission	03/31/2018
Study completion	11/31/2030
Final report submission	11/31/2031

Postmarketing Commitment:

- 7) 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.

Final report submission	03/31/2017
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/s/

KENDALL A MARCUS
02/06/2017