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RESEARCH**

APPLICATION NUMBER:

761032Orig1s000

CROSS DISCIPLINE TEAM LEADER REVIEW

Cross-Discipline Team Leader Review

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| Date | September 16, 2016 |
| From | David Kettl, MD |
| Subject | Cross-Discipline Team Leader Review |
| NDA/BLA # | BLA 761032 |
| Supplement# | (Related IND: 104671) |
| Applicant | Valeant Pharmaceuticals North America LLC |
| Date of Submission | November 16, 2015 |
| PDUFA Goal Date | November 16, 2016 |
| Proprietary Name / Non-Proprietary Name | Siliq (brodalumab) |
| Dosage form(s) / Strength(s) | Injection, for subcutaneous use |
| 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 |
| Recommendation on Regulatory Action | <i>Approval, with REMS with ETASU and labeling to include a Boxed Warning for suicide related events</i> |
| Recommended Indication(s)/Population(s) (if applicable) | <i>Brodalumab should only be used in patients who have failed to respond, or lost response, to other biologic therapies and participate in the REMS with ETASU risk mitigation strategies as described below</i> |

1. Benefit-Risk Assessment

Valeant Pharmaceuticals submitted a BLA for SILIQ, (brodalumab) for subcutaneous injection at a dose of 210mg at O, 1, and 2 weeks with subsequent maintenance therapy of Q2W injections, for the treatment of moderate to severe plaque psoriasis in adults who are candidates for systemic therapy or phototherapy. The PDUFA goal date is November 16, 2016.

Benefit-Risk Summary and Assessment

Brodalumab is a human, IgG2 monoclonal antibody that selectively binds and blocks signaling through the IL 17 receptor. This new antibody is being developed for the treatment of moderate to severe plaque psoriasis. While plaque psoriasis can be serious, burdensome and significantly impact patient quality of life, particularly in those patients with substantial involvement of skin surfaces, there is no mortality risk with this disease.

Phase 3 trials included 4300 subjects and successfully demonstrated substantial efficacy at the primary endpoints. Approximately 80% of subjects had success in both a static Physician Global Assessment score (sPGA) reduction to “clear” or “almost clear” as well as a 75% reduction in Psoriasis Area and Severity Index(PASI) score. Notably, about 40% of subjects experienced clearance of their psoriasis at the primary time point of 12 weeks. This was a significant difference compared to the active comparator in two of the phase 3 trials, ustekinumab, an IL 12/23 antagonist approved for the same psoriasis indication in 2009.

The safety experience for the expected adverse reactions of serious infections, neutropenia, and potential malignancy risk from immunosuppression did not identify any substantial concerns for safety compared to other antibody products in the class. However, during the latter part of the phase 3 psoriasis program, 4 completed suicides were reported, all on brodalumab with none in the placebo or ustekinumab arms. Two additional suicides were noted in brodalumab trials for other indications, one in rheumatoid arthritis and one in psoriatic arthritis. Amgen, the sponsor at that time, elected to terminate further development in May, 2015, and closed all brodalumab trials due to the risk of suicide and suicidal ideation. This number of completed suicides is unprecedented in psoriasis trials, or trials for any indication in this Division.

Additionally, an imbalance of cardiovascular deaths and other events were observed in the brodalumab arms. Though detailed review did not identify a causal relationship, and lack of data prevented the Agency cardiology review from reaching any definitive conclusion, cardiovascular events on brodalumab will require additional monitoring.

There were no substantive issues identified in the CMC, nonclinical, or clinical pharmacology reviews of this antibody product. The central issue for this application is whether the risk of suicide and suicidal ideation is so significant that it should preclude approval for the treatment of moderate to severe plaque psoriasis, which typically does not have fatal complications.

The primary clinical review, as well as consultative reviews from the Division of Psychiatry Products and the Division of Epidemiology I in

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OSE, concludes that the product should not be approved due to this risk with the current information available. The DPP review recommends a pre-approval clinical trial 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. The Division of Pharmacovigilance in OSE concluded that the product could be approved with adequate labeling.

No treatment to date has been universally successful in providing clearance of psoriatic skin lesions in affected patients. Additionally, even in patients who have a substantial response to one or more systemic therapies, most have a gradual waning of treatment effect over time and many patients need to rotate through various available therapies over time for this chronic, typically lifelong indication. The degree of treatment effect observed in the brodalumab program indicate that there are likely patients who would accept the known risks in order to achieve largely clear skin, particularly when they might have failed to respond, or inadequately responded to other systemic therapies.

Following extensive, multidisciplinary review of the data, Advisory Committee discussion, and internal discussions which included presentations at the REMS Oversight Committee, this CDTL review concludes that brodalumab should be made available with labeling sufficient to describe and inform this risk, as well as a REMS with ETASU (elements to assure safe use) to insure that prescribers understand and acknowledge the risks, and document that patients who use brodalumab are fully consented regarding the benefits and potential risks, even the possibility of a fatal risk.

While it is unlikely that a prospective trial could be large enough or long enough to definitively quantify the risk of rare events such as suicide and suicidal behavior, a post marketing clinical trial to prospectively assess these events is recommended due to the limitations of the truncated clinical development program.

| Dimension | Evidence and Uncertainties | Conclusions and Reasons |
|---------------------------------------|---|--|
| Analysis of Condition | <ul style="list-style-type: none"> Psoriasis is a chronic inflammatory skin disease characterized by patches of red, itchy, and scaly abnormal skin. Plaque psoriasis is by far the most common type, with other, less common types characterized as guttate, inverse, pustular, and erythrodermic. Psoriasis is likely a genetic disease with cycles of inflammation and cellular proliferation resulting typically resulting in clinical skin plaques. | <p>There is no curative therapy. Severe disease can often require lifelong treatment, but is not life threatening. Patients report significant impacts on quality of life assessments.</p> |

| Dimension | Evidence and Uncertainties | Conclusions and Reasons |
|--|--|--|
| <p>Current Treatment Options</p> | <ul style="list-style-type: none"> Mild disease may not require any treatment beyond topical therapy with corticosteroids or synthetic vitamin D products, but systemic treatments may be required for more widespread, chronic, or advanced disease. These include adalimumab, etanercept, infliximab (all TNF blockers), secukinumab and ixekizumab, IL 17 inhibitors, and ustekinumab, an IL12/23 inhibitor. Other approved systemic psoriasis therapies include acitretin, methotrexate, cyclosporine, and apremilast. Phototherapy, either PUVA (UVA light combined with the psoralen methoxsalen) or UVB light therapy (narrow or broadband) is also an appropriate first line or adjunctive treatment for moderate to severe psoriasis patients. | <p>No treatment has been shown to be universally effective, with PASI 75 assessed treatment effects of systemic products ranging from about 30% (apremilast) to about 89% (ixekizumab). Tolerance or waning of treatment response over time is not uncommon for systemic treatments. Almost all treatments have some degree of immunosuppression that may increase the risk of systemic infections, and potentially development of malignancies.</p> |
| <p>Benefit</p> | <ul style="list-style-type: none"> The clinical trials of brodalumab in chronic plaque psoriasis provided substantial evidence of effectiveness. The efficacy of brodalumab was evaluated in three pivotal Phase 3 trials, two of which included an active comparator (ustekinumab) arm. In all three trials, for the comparison of brodalumab against placebo at Week 12, the co-primary endpoints were the proportion of subjects achieving PASI 75 response (i.e., $\geq 75\%$ reduction in PASI score) and an sPGA of 0 or 1. Secondary endpoints were PASI 100, sPGA score of 0, and Psoriasis Symptom Inventory (PSI) responder (i.e., total score ≤ 8, with no item score > 1) at Week 12. In Trials 03 and 04, for the comparison of brodalumab against ustekinumab at Week 12, the primary endpoint was PASI 100 (i.e., sequentially tested the brodalumab 210 mg vs. ustekinumab, then weight-based brodalumab vs. ustekinumab) with secondary endpoints of PASI 100 (brodalumab 140 mg vs. ustekinumab) and PASI 75 (weight-based brodalumab vs. ustekinumab). For the comparison against placebo, both brodalumab doses were superior to placebo ($p < 0.001$) for the co-primary as well as the secondary endpoints in each of the pivotal trials. For the comparison | <p>Two adequate and well controlled trials provided adequate evidence of effectiveness in the population of moderate to severe psoriasis under the proposed conditions of use. The trials were adequate and well-controlled. The PGA response of 0 or 1 was 76%, 79% and 80% and the proportion of PASI 75 responders were 83%, 86% and 85% respectively for the registration trials. The observed treatment effect with brodalumab treatment is similar, or slightly higher than the best performing treatments currently available. Nearly 43% of brodalumab treated subjects achieved disease clearance (as assessed by PASI 100), the most clinically meaningful endpoint for patients, by week 12 of treatment. This was slightly better than the approximately 40% who achieved disease clearance with ixekizumab treatment at the primary endpoint.</p> |

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| Dimension | Evidence and Uncertainties | Conclusions and Reasons |
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| | <p>against ustekinumab, brodalumab 210 mg and the weight-based dosing of brodalumab were superior to ustekinumab (p<0.001) for the primary endpoint of PASI 100 response.</p> | |
| <p><u>Risk</u></p> | <ul style="list-style-type: none"> The proposed size of the safety database appeared adequate for the expected significant risks of serious infections and potential malignancies, and was similar to other development programs for systemic, monoclonal antibody drug products for psoriasis. However, clinical trials were abruptly halted in phase 3 upon identification of a significant difference in suicidal ideation and completed suicides in brodalumab treated subjects. Consequently, the long term, ongoing experience typically provided for antibody treatments for psoriasis at the time of BLA submission was truncated for this application. Nonetheless, across all brodalumab development programs, a total of six completed suicides occurred, of which one was possibly an unintentional overdose despite the medical examiner ruling of suicide. Four completed suicides were adjudicated in the psoriasis (PsO) program, one in rheumatoid arthritis (RA) and one in psoriatic arthritis (PsA) programs. All suicides occurred in subjects exposed to brodalumab. Clinical trial evaluations were adequate to assess the risks for the expected adverse reactions of serious infections, neutropenia, Crohn’s disease, and cardiovascular events. Numerically, brodalumab had the highest rate of MACE across products, and also the numerically highest rate of CV death. | <p>Definitive conclusions regarding adverse events of rare frequency, such as suicide and suicidal ideation, are not possible given the current information. Neuropsychiatric events are not uncommon in psoriasis patients, and factors that influence suicidal behavior are numerous and complex.</p> <p>However, the numerical findings for these events in the brodalumab programs appear to be greater than all other antibody programs for psoriasis together, and there is an obvious need for patients and prescribers alike to be aware of this issue and to provide true, informed consent and acknowledgement of this risk with brodalumab treatment.</p> <p>Other safety findings, while serious, have been observed in other related psoriasis programs and labeling should be adequate to address the risks of these events.</p> |
| <p><u>Risk Management</u></p> | <ul style="list-style-type: none"> The conclusion of the primary clinical review, as well as consultative reviews from the Division of Psychiatry Products, and the Division of Epidemiology from OSE recommend a Complete Response for this application. The Division of Pharmacovigilance in OSE, and the Division of Cardiorenal Products did not concur with this | <p>The REMS Oversight Committee, with input from the CDER and OND directors, recommended the following risk mitigation strategies as a condition of application approval:</p> |

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| Dimension | Evidence and Uncertainties | Conclusions and Reasons |
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| | <p>recommendation.</p> <ul style="list-style-type: none"> This CDTL review recommends approval of this application with a boxed warning, other labeling considerations such as limitations of use to limit brodalumab to those who have previously failed to respond, or lost response to other biologic therapies, and a REMS with ETASU to insure that prescribers and patients are fully informed and consented regarding the risk of a fatal adverse event while being treated for a disease, though serious and impactful on patients, that does not have fatal outcomes or complications. | <p>Optimized labeling would include:</p> <ul style="list-style-type: none"> A Boxed Warning discussing the potential increased risk of suicidality with brodalumab A Limitation of Use that the brodalumab should only be used in patients who have failed to respond, or lost response, to other biologic therapies A recommendation to discontinue therapy in patients who do not achieve an adequate response within 12 weeks <p>The REMS with ETASU would include:</p> <ul style="list-style-type: none"> Physician certification: A ‘streamlined’ process by which physicians learn of the risk of suicidality, acknowledge their understanding of the risk, and agree to counsel patients on the risk. Pharmacy certification: To ensure that brodalumab prescribers are certified. Safe use conditions: Patients will need to sign an acknowledgement form asserting that they were counseled by their physician on the potential risk of suicidality, and that they understand that this is a potential risk associated with brodalumab treatment. |

2. Background

Psoriasis is a common, chronic inflammatory skin disease characterized by patches of red, itchy, and scaly abnormal skin. Plaque psoriasis is by far the most common type, with other, less common types characterized as guttate, inverse, pustular, and erythrodermic. Psoriasis is likely a genetic disease with cycles of inflammation and cellular proliferation resulting typically resulting in clinical skin plaques. The prevalence of psoriasis in the US is estimated at around 3.1% among adults, and approximately 18% of patients diagnosed with psoriasis are estimated to develop moderate to severe disease.

There is no curative therapy. Mild disease may not require any treatment beyond topical therapy with corticosteroids or synthetic vitamin D products, but systemic treatments may be required for more widespread, chronic, or advanced disease. These include adalimumab, etanercept, infliximab (all TNF blockers), secukinumab and ixekizumab, which are IL 17 inhibitors, and ustekinumab, an IL12/23 inhibitor. Other approved systemic psoriasis therapies include acitretin, methotrexate, cyclosporine, and apremilast. Severe or widespread disease can often require lifelong treatment.

IL-17A is a naturally occurring cytokine that is involved in normal inflammatory and immune responses and plays a role in the pathogenesis of plaque psoriasis. Elevated levels of IL-17A are found in psoriatic plaques and two precedent applications with IL-17A antagonists, secukinumab and ixekizumab, have been approved for the treatment of adult patients with moderate to severe psoriasis. The mechanism of action for brodalumab is slightly different than the two IL-17 products previously approved. Brodalumab acts as a receptor blocker, preventing interaction with IL-17A.

The proposed brodalumab dosing regimen is 210 mg subcutaneously at weeks 0, 1, and 2, followed by 210 mg every 2 weeks thereafter. The proposed drug product presentation is a 1.5 mL pre-filled syringe.

The IND was submitted August 27, 2009. No formal End of Phase 2 meeting was conducted for this application. No Special Protocol Assessment was requested or provided for any of the Phase 3 trials. A pre-BLA meeting was conducted on October 21, 2015.

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Following the 5/13/2015 meeting with Amgen to discuss the Suicidal Ideation and Behavior (SIB) risk across the brodalumab programs, Amgen (the development and commercial partner to Astra Zeneca) decided to discontinue further development of brodalumab and terminated all ongoing studies. On 8/31/2015, Astra Zeneca and Valeant had entered a new license agreement for the development of brodalumab.

The Agency had another Pre-BLA meeting on 10/21/2015 with the new sponsor, Astra Zeneca, to discuss the Agency's concern regarding the SIB observed in the brodalumab development program.

On 11/16/2015, the BLA was submitted to the Agency, and on 4/1/2016, the Agency received a notification from Valeant Pharmaceuticals Luxembourg regarding the transfer of ownership of the BLA from Astra Zeneca.

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

Critical to the consideration of this application is consideration of the therapeutic context for treatment of moderate to severe psoriasis, and the relative risks of the current armamentarium. Brodalumab has substantial efficacy, as high as, or slightly higher than several recently approved products. Systemic treatments for psoriasis include:

| Small Molecule Therapies | | |
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| Product | Class | Warnings/Precautions |
| Acitretin | retinoid | teratogen; hepatotoxicity; hyperostosis; lipid effects |
| Methotrexate | folate antagonist | teratogen; liver fibrosis/cirrhosis; hematologic toxicity; interstitial pneumonitis; opportunistic infections |
| Cyclosporine | inhibits IL-2 | hypertension; nephrotoxicity; serious infections; malignancy |
| Apremilast | phosphodiesterase 4 inhibitor | Depression; weight decrease; drug-drug interactions |
| Biologic Therapies | | |

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| Etanercept | TNF α -blocker | serious infections (including TB); malignancy; central nervous system demyelinating disorders; hematologic events (pancytopenia); reactivation of hepatitis B; autoimmunity |
| Adalimumab | TNF α -blocker | Serious infections (including TB); malignancy; reactivation of hepatitis B; demyelinating disease; hematologic reactions (pancytopenia); autoimmunity |
| Infliximab | TNF α -blocker | serious infections (including TB); malignancy; demyelinating disease; hepatotoxicity |
| Ustekinumab | interleukin-12 and -23 antagonist | serious infections; malignancy; reversible posterior leukoencephalopathy syndrome |
| Secukinumab | Interleukin-17A antagonist | Serious infections; TB, exacerbation of Crohn's, hypersensitivity |

For 10-15 years, TNF blockers were the standard of care for patients requiring systemic treatment, either due to severity of the psoriasis lesions, body surface area of involvement, or both. Over the last five years, ustekinumab, secukinumab, and, earlier this year, ixekizumab, have been approved for this indication. These products have slightly better treatment effects and less observed toxicities to date than products in the TNF blocker class. In addition, at least 5 other systemic biologic therapies are expected to be submitted to the Agency in the next few years for psoriasis.

While most of these products can have a remarkable effect on the course of psoriasis, none are universally effective or curative, and most of an eventual waning of treatment effect over time with few patients remaining on one therapy over the course of their lifelong, waxing and waning clinical course of psoriasis.

Brodalumab, has outlined in the efficacy section below, has substantial efficacy, and successfully met endpoints related to 100% clearance of psoriasis lesions. The expected toxicities of serious infections, neutropenia, and potential malignancies, were not observed to any significant degree in the clinical development program.

However, by early 2015, it was observed that six completed suicides had been reported in brodalumab trials, all in active brodalumab arms. Additionally, 34 subjects had 39 Suicidal Ideation and Behavioral (SIB) events (SIB is defined as completed suicides, suicidal ideation, and suicidal behaviors) in the brodalumab trials. The Phase 3 clinical trials were then terminated by Amgen in May, 2015 as they considered that potential labeling to inform these events would have an adverse business impact on this product.

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Multiple reviews of this issue have been completed by various groups within the Agency to validate and characterize the risk of these events. The risk/benefit assessment and approvability determination has not been unanimous in either direction.

The primary clinical review by Dr. Chiang, as well as the consultative reviews from the Division of Psychiatry Products, and the Division of Epidemiology from OSE recommends a Complete Response for this application. The Division of Pharmacovigilance in OSE, and the Division of Cardiorenal Products did not concur, or found insufficient evidence to support this recommendation. The majority of the members of the Dermatologic and Ophthalmic Drugs Advisory Committee, who met in July 2016 to publicly discuss this application, agreed that the product could be approved, though certain members recommended a registry and/or boxed warning to inform prescribers and patients of the observed risks.

Given the nature of life long psoriasis treatment discussed above, this CDTL review disagrees with the primary clinical review by Dr. Chiang. With adequate informed consent, and appropriate follow-up and clinical monitoring, there is likely a subset of moderate to severe psoriasis patients who would find this risk/benefit acceptable.

I conclude that a boxed warning for suicide and suicidal ideation/behavior is indisputably indicated for this action. In addition, review by DRISK recommends a REMS with ETASU (Elements to Assure Safe Use) to assure that prescribers and patients are adequately informed, consented, and appropriately used in patients who have failed to respond, or lost response, to other biologic therapies for moderate to severe plaque psoriasis. This level of risk mitigation is adequate given the know risks of brodalumab and will allow this effective product to find its place in the marketplace for treatment of moderate to severe psoriasis.

3. Product Quality

The multidisciplinary OPQ review recommends approval of the application, pending final responses to several pending information requests. A description of the pertinent CMC issues from their review follows:

Brodalumab is a full length recombinant, human IgG2 monoclonal antibody and consists of two heavy chains that are each composed of 442 amino acids and two light chains that are each composed of 214 amino acids. The production cell line for brodalumab was derived from CHO^{(b) (4)} cells ^{(b) (4)}.

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The brodalumab DS is manufactured at (b) (4). The drug product is manufactured and filled into the primary container closure at (b) (4). No inspections specific to brodalumab drug product were conducted. The compliance status of the production facility associated with the manufacture of brodalumab DP is acceptable based on recent previous inspections and district recommendation. Secondary labelling and packaging is performed at (b) (4). The compliance status of the secondary labelling and packaging facility and drug product testing facilities were also acceptable.

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) and is intended for subcutaneous dosing.

Each sterile pre-filled 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. The drug substance is stored in (b) (4).

The container closure system is suitable for brodalumab manufacturing based on stability data and maintenance of closure integrity. The dating period for the drug substance is (b) (4) months when stored at (b) (4).

There are no special product quality labeling recommendations as compared to those used for similar marketed protein products.

There are no novel excipients.

A pre-licensure inspection (PLI) of the biologics drug substance manufacturing facility was conducted at (b) (4) (b) (4) from (b) (4) by DMA reviewers (Maria Candauchaon and Maria Jose Lopez-Barragan), DIA reviewer (Donald Obenhuber) and OBP product quality reviewers (Willie Wilson and Joanna Zhou). The PLI covered the following five Quality Systems: Quality Procedures, Facilities and Equipment, Materials Management, Production Processes and Contamination Prevention, and Laboratory Controls.

A three-item 483 was issued; the 483 issues were related to the standard operating procedures for the (b) (4) (b) (4) integrity test, microbial control for the (b) (4) used for drug substance formulation and microbial control of (b) (4) after storage. The initial recommendation for the classification of the inspection is VAI.

The requirement for conducting a PLI for the drug product manufacturing facility was waived based on a facility profile evaluation, which was found to be acceptable.

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The OPQ review concludes that “With the exceptions noted below, the data submitted in this Biologics License Application support the conclusion that the manufacture of SILIQ (brodalumab) 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 the parameters recommended by FDA. The conditions used in manufacturing have been sufficiently validated, and a consistent product has been manufactured from the multiple production runs presented.”

The following issues are pending as of the date of this CDTL review and need to be addressed prior to the Action Date. The review of these issues will be included in an OPQ Addendum to the 7/1/2016 BLA review.

1. Inclusion of cIEF analysis as part of the lot release and post-approval stability specifications for drug substance (DS) and drug product (DP).
2. Inclusion of the bioassay as part of the lot release and post-approval stability specifications for DS and DP.
3. Updating of the (b) (4) (in-process testing) to account for the differences observed between the (b) (4)
4. Inclusion of the reduced and non-reduced CE-SDS methods as part of the DS and DP lot release and stability specifications or providing appropriate justifications for their removal.
5. Providing acceptable process characterization and/or validation data to support the (b) (4) ranges for each (b) (4) step or tightening the ranges to those supported by process and (b) (4) validation studies.
6. Providing acceptable data to support the (b) (4) with respect to brodalumab quality or revising the action limit to reflect historical experience.
7. Providing the specific strategies that will be used to monitor and control variation in brodalumab product quality due to changes in (b) (4).
8. Updating of the future WCB qualification protocol to include appropriate acceptance criteria or removal of the protocol from the BLA.

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9. Tightening of or modification of the proposed potency criterion for qualification of future primary and working reference standards or removal of these protocols from the BLA.
10. Providing evidence of successful method validation or transfer of each test method at each facility identified as a testing facility or specifying the appropriate test(s) performed at each facility in Section 3.2.P.3.1 and Form 356h.
11. Providing information to justify the use of Ph.Eur./JP (b) (4), rather than USP/NF (b) (4), as a drug product excipient.
12. Updating of Sections 3.2.S.7 and 3.2.P.8 with appropriate drug substance and drug product expiry periods that are supported by stability data from fully representative lots.

The OPQ review recommends the following PMR and PMC's:



Final determination of the PMR/PMC recommendations will be identified in the OPQ addendum in advance of the action and will be determined by the final information submitted by the applicant.

4. Nonclinical Pharmacology/Toxicology

The nonclinical review by Carmen Booker, PhD concludes that there are no outstanding approvability issues related to nonclinical elements for this application. Labeling changes for Sections 8, 12 and 13 of product labeling are proposed to be communicated the applicant if an approval action is substantiated.

No independent safety pharmacology studies were conducted. Safety pharmacology endpoints were evaluated in repeat-dose toxicity studies in cynomolgus monkeys.

No single dose toxicity studies were submitted. The sponsor conducted a 1-month toxicity study of brodalumab using SC and IV dosing in cynomolgus monkeys. Five animals per group were administered 0, 25, 90 or 350 mg/kg/dose brodalumab once weekly for four weeks. Brodalumab was well tolerated at all dose levels.

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Based on ICH S6 (Guideline for the Safety Evaluation of Biotechnology-Derived Pharmaceuticals) guidelines, no genetic toxicology studies were conducted with brodalumab.

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

The applicant submitted literature to describe the carcinogenic potential of brodalumab, an IL-17RA antagonist. The role of IL-17 in angiogenesis, tumor promotion and human carcinogenicity is uncertain as the literature is conflicting. The majority of the references suggest there is no increased carcinogenic potential from IL-17RA or IL-17 inhibition. No nonclinical studies to assess the carcinogenic potential of brodalumab are recommended.

In cynomolgus monkeys, there were no effects on fertility parameters such as reproductive organs or sperm analysis following subcutaneous administration of brodalumab at dose levels up to 90 mg/kg/week for six months (26 times the MRHD on a mg/kg basis).

In a combined embryofetal development and pre- and post-natal development study, no adverse developmental effects were observed in infants born to pregnant monkeys after subcutaneous administration of brodalumab during organogenesis through parturition at doses up to 26 times the maximum recommended human dose. No brodalumab-related effects on embryofetal toxicity or malformations, or on morphological, functional or immunological development were observed in infants from pregnant monkeys.

Dr. Booker, with concurrence from the Pharm/Tox supervisor, Dr. Barbara Hill, concludes that the application is approvable for the treatment of moderate-to-severe plaque psoriasis from a pharmacology/toxicology perspective. There are no recommended nonclinical post marketing requirements or commitments.

5. Clinical Pharmacology

The clinical pharmacology review by Jie Wang, PhD, concludes that from a Clinical Pharmacology standpoint, the BLA is acceptable to support the approval of brodalumab for the treatment moderate to severe plaque psoriasis in adult patients contingent upon agreement on labeling.

Dr. Wang's review describes the principal PK and immunogenicity findings of the application as follows:

The primary pharmacodynamic finding was that serum levels of IL-17A were increased after receiving 140 mg or 210 mg brodalumab treatment compared to the pretreatment levels in subjects with moderate to severe plaque psoriasis. The increase in trough serum IL-17A levels at steady state appeared to be dose-dependent: 210 mg every 2 weeks (Q2W) dosing was associated with a greater increase in trough serum levels of IL-17A than 140 mg Q2W dosing.

Beyond the IL-17A levels, there are no data available for evaluating the impact of brodalumab treatment on serum levels of other cytokines. Theoretically, increased serum levels of IL-17A may modulate serum level of other cytokines, including IL-6. The relationship between these pharmacodynamic activities and the mechanism(s) by which brodalumab exerts its clinical effects is unknown. Though IL-6 has been implicated in some literature reports in the process of depression and/or suicide, no conclusions can be made on the basis of the data obtained in this application.

Following subcutaneous administration, the estimated brodalumab bioavailability was approximately 55% based on population PK modeling.

Brodalumab exhibited non-linear PK with brodalumab exposures increasing in a greater than dose-proportional manner and the clearance of brodalumab decreasing with increasing dose.

Age, sex, or race did not significantly influence the PK of brodalumab. On the other hand, brodalumab clearance and volume of distribution increase as body weight increases.

As is typical for monoclonal antibodies, hERG and dedicated in vivo QT studies are not required due to the size of the antibody.

Drug interactions:

The observed drug-drug interaction could be clinically relevant for CYP3A4 substrate drugs that have narrow therapeutic index.

- CYP3A4 substrates: 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. We note that the effect of peak brodalumab concentration occurring 3 days post dose has not been evaluated.
- Substrates of other CYP450 isozyme: Clinical studies have not been conducted.

Immunogenicity:

- Following up to 52 weeks of treatment, 2.7% (120/4447) of subjects with psoriasis developed brodalumab treatment-emergent ADA across seven clinical trials; and 2.1% (86/4058) of subjects developed brodalumab treatment-emergent ADA in Phase 3 trials.
- Of the subjects who developed ADA, none (0%) were classified as positive for neutralizing antibodies. However, the incidence of neutralizing antibodies development could be underestimated because the assay to test for neutralizing antibodies has limitations in detecting neutralizing antibodies 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.

Dr. Wang concludes that the dose and dosing regimen are adequately supported. No individualization of doses was recommended, unlike for the recently approved application for secukinumab for the same indication. Although body weight was identified as a significant covariate that impacted brodalumab exposure and body weight also showed an effect on efficacy, alternative dosing regimens adjusting for body weight is not recommended by his review based on the available data.

The clinical pharmacology review specifically examined the submitted PK data related to the subjects with completed suicides. The review examined whether there is a correlation between the PK or pharmacodynamic effects of brodalumab and SIB in subjects with psoriasis.

Dr. Wang's review concludes that because the serum brodalumab concentrations at the exact time when the suicide events occurred are unknown, it is not feasible to evaluate whether there is any potential relationship between the systemic brodalumab exposure and the completed suicide. Nonetheless, he notes that the brodalumab concentrations in these subjects at the time of event are likely to vary widely given the time after the last brodalumab dose spanned a large range (14-58 days). Additionally, the available PK data up to Week 52 of the Phase 3 trials showed that the brodalumab exposure in these 4 subjects were not remarkable, i.e., they were not among the highest in the study population. The review concludes "it is unlikely that the suicidal events could be attributable to high brodalumab exposure in these 4 subjects either throughout the study or at the time of event."

However, the review also states that "It is biologically plausible that brodalumab treatment may cause SIB due to cytokine regulations because immune dysregulation may have implications in psychiatric disorders." This reviewer's understanding is that these relationships are not well characterized to date and the submitted data available in this application is insufficient to provide any definitive understanding of downstream cytokine impacts on neuro-psychiatric events.

The clinical pharmacology review does not recommend a Complete Response. The clinical pharmacology assessment is that "The limited available clinical data did not suggest a direct correlation between brodalumab exposure and up-regulation of serum IL-17A levels and completed suicide or SIB." Their recommendation is to "recommend the use of product labeling to communicate this potential risk."

There are no Clinical Pharmacology-specific PMC or PMR recommendations. Proposed labeling changes for sections 5, 7 and 12 will be communicated to the sponsor assuming an eventual approval action.

6. Clinical Microbiology

No microbiology claims were evaluated or asserted for this application.

7. Clinical/Statistical- Efficacy

The primary Agency clinical review was conducted by Dr. Gary Chiang, and the Biostatistical review was conducted by Dr. Carin Kim.

The brodalumab psoriasis development program included 12 studies providing clinical and clinical pharmacology data for the proposed indication:

Seven Phase 1 PK/PD studies in healthy subjects and subjects with psoriasis:

- Two PK studies in healthy subjects (20060279 and 20120337),
- One intrinsic factor PK/PD study in healthy subjects and subjects with psoriasis (KHK4827-001)
- One extrinsic factor PK study in subjects with psoriasis (20110184)
- One PK device performance study (20110106)
- Two PK comparability studies in healthy subjects (20090480 and 20130307)

Two Phase 2 dose ranging studies in subjects with psoriasis

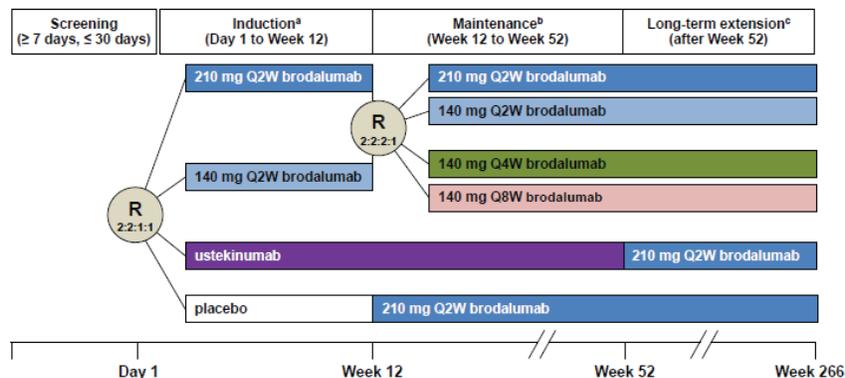
- One dose ranging study in subjects with psoriasis (20090062)
- One dose ranging study in Japanese subjects with psoriasis (KHK4827-002)

Three Phase 3 efficacy/safety pivotal trials in subjects with psoriasis

- One placebo-controlled study (20120102)
- Two active comparator-controlled and placebo-controlled studies (20120103 and 20120104)

A schematic depiction of the Phase 3 trials 03 and 04 provided by the applicant is reproduced below:

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R = randomization; Q2W = every 2 weeks (with an additional loading dose 1 week after initiation of brodalumab); Q4W = every 4 weeks; Q8W = every 8 weeks
^a In the induction phase, subjects were randomized in a 2:2:1:1 ratio to receive brodalumab 210 mg Q2W, brodalumab 140 mg Q2W, ustekinumab, or placebo.
^b At the week 12 visit, subjects originally randomized to the brodalumab arms were rerandomized (2:2:2:1) into the maintenance phase to receive brodalumab 210 mg Q2W, 140 mg Q2W, 140 mg Q4W, or 140 mg Q8W. Subjects originally randomized to ustekinumab continued to receive ustekinumab and those originally randomized to receive placebo received brodalumab 210 mg Q2W. Subjects who did not attend their week 12 visit did not receive any further investigational product.
^c At week 52, subjects who were originally randomized to ustekinumab were to begin receiving brodalumab 210 mg Q2W.

The safety and efficacy of brodalumab was evaluated in three pivotal Phase 3 trials with two trials (Trials 03 and 04) that included an ustekinumab arm for demonstration of superiority to this active comparator. All trials enrolled subjects 18 to 75 years of age and older with stable moderate to severe plaque psoriasis diagnosed at least 6 months before the first dose of investigational product. The enrolled subjects had plaque-type psoriasis with Psoriasis Area and Severity Index (PASI) score ≥ 12 , static Physician’s Global Assessment (sPGA) score of at least 3, and body surface area (BSA) involvement $\geq 10\%$ at baseline.

In all three trials, for the comparison of brodalumab against placebo at Week 12, the coprimary endpoints were the proportion of subjects achieving PASI 75 response (i.e., $\geq 75\%$ reduction in PASI score) and a sPGA score of 0 or 1. These endpoints are typically recommended by the Agency for systemic antibody products. Secondary endpoints were PASI 100 (i.e., 100% reduction in PASI score), sPGA score of 0, and Psoriasis Symptom Inventory (PSI) responder at Week 12. In Trials 03 and 04, for the comparison of brodalumab against ustekinumab at Week 12, the primary endpoint was PASI 100.

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For the comparison of each brodalumab dose against placebo, both brodalumab doses were superior to placebo for all co-primary as well as secondary endpoints at Week 12 (p<0.001). However, for the comparison against ustekinumab, only the brodalumab 210 mg dose and the weight-based brodalumab dose were superior to ustekinumab for the protocol-specified primary endpoints of PASI 100 (p<0.001).

The following is reproduced from Dr. Kim's review:

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

| | | Brodalumab 210 mg | Brodalumab 140 mg | Placebo | Ustekinumab | Weight- based ⁽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

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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)

The demographics at baseline in the Phase 3 trials were balanced across the treatment arms within each trial; however, in Trial 02, the prior biologic use was about 46% compared to 29% and 25% in Trials 03 and 04, respectively. Approximately 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 with about 72% of the subjects who were ≤ 100 kg at baseline. For all Phase 3 trials, the baseline median PASI was 17.4 with ranges of 12 to 72 (note that there was one subject in Trial 03 with a baseline PASI of 9.4), and the median body surface area (BSA) was about 21 with ranges of 10 to 97. Approximately 58%, 37%, 5% of the subjects were of scores 3 (moderate), 4 (severe) and 5 (very severe) at baseline, respectively.

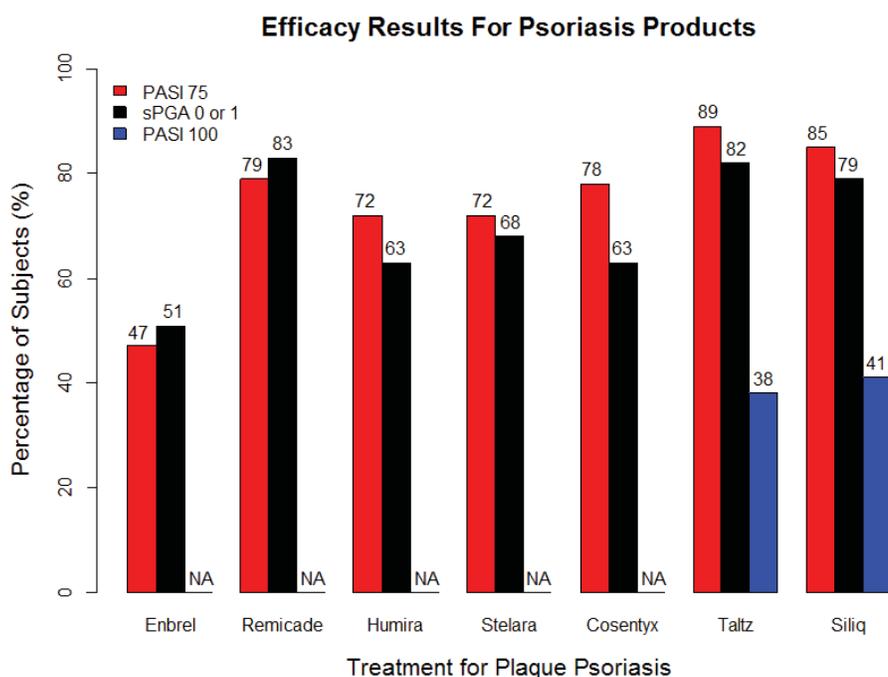
Trials 03 and 04 evaluated maintenance of sPGA success at Week 52 but the maintenance endpoint was not a part of the multiplicity testing strategy. In an advice letter dated 6/6/2012, the Agency stated that there was no agreement on a labeling claim for the proposed maintenance endpoint, and that the goal of assessment of maintenance regimen should be to identify the regimen with a favorable efficacy and safety profile. Nonetheless, the 210mg Q2W dosing appears to have the most efficacious result in response to maintenance out to 52 weeks, and appears to be more consistent over time than other antibody products for psoriasis.

Trial 02 was conducted in 6 countries; Trial 03 was conducted in 10 countries; Trial 04 was conducted in 11 countries. These included the US, Canada, Australia, and several countries in Europe. In all three trials, the treatment effects for sPGA response and PASI 75 were generally consistent across the countries, except for the US which sPGA and PASI 75 responses were slightly lower than those of the other countries.

Dr. Kim's review concludes that "There were no major statistical issues affecting the overall efficacy conclusions. The treatment effects were large and consistent across trials, and the amount of missing data was relative small ($\leq 6\%$) at Week 12."

Both the clinical and Biostatistical reviews concur that the Applicant has provided the substantial evidence of effectiveness required by law [21 CFR 314.126(a)(b)] to support approval. There were no issues related to endpoints, missing data, or statistical analyses that would impact this conclusion.

While actual comparisons to brodalumab were obtained in the development program only with ustekinumab, the following table from Dr. Kim’s review is reproduced below to provide context for the risk/benefit discussion which follows below in this review. Limitations on issues which face cross study comparisons are acknowledged, but this table of efficacy results from different trials and development programs is useful to understand why certain psoriasis populations might be accepting of brodalumab therapy, particularly when other systemic products have failed or demonstrated waning efficacy over time in chronic use.



8. Safety

Outside of neuropsychiatric events, the overall adverse event profile for brodalumab did not differ substantially from placebo, or the ustekinumab arms in two Phase 3 trials. The most common AE's at both 12 weeks and 52 weeks were nasopharyngitis, URI's, headache and arthralgias. Serious AE's overall occurred with similar frequency across all arms at the 12 week time point, with the most common events being cellulitis, appendicitis, and gastroenteritis.

Fatal events were increased with brodalumab treatment, with 23 deaths (12 cardiovascular, 4 completed suicides, 3 accidental deaths, and 4 other events) compared with 2 deaths in the ustekinumab arms (MI, and pancreatic cancer). The applicant contends, on the basis of adjusted rate per 100 patient year statistical analyses, that, rates were similar at 52 weeks.

Cardiovascular events were nominally increased, but the review from the Division of Cardiorenal Products by Dr. Senatore Fortunato concluded that no specific safety signal could be identified from the submitted data: "The number of MACE occurrences in the 12-week double-blind period of the psoriasis trials was too small to draw a conclusion about the risk of MACE due to brodalumab compared to placebo or active comparator. In the 52-week follow-up period of the psoriasis trials, there was a numerically 3.5-fold higher follow-up-time adjusted incidence rate of adjudicated MACE for brodalumab compared to ustekinumab. This suggested a potential safety signal but the incidences were low, and there may have been an ustekinumab contribution to the brodalumab arm due to switching beyond the 12-week double blind period."

If no neuropsychiatric events had occurred in the brodalumab development program, these safety events would not have been disqualifying for approval, and could be addressed solely through product labeling, and an approval action would likely have been recommended.

The primary safety issue in this application relates to analyses of the data from reports of completed suicide and suicidal ideation/behavior which is unique to date for systemic psoriasis applications. The expected adverse reactions related to

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immunosuppression such as serious infections, cardiovascular events and malignancies were determined not to be significant enough to alter the risk/benefit determination for approval of the application.

The safety record of brodalumab for psychiatric related events in the psoriasis development program has been extensively reviewed by multiple divisions within the Agency due to the number of completed suicides identified during the latter stages of the Phase 3 trials. Consultative reviews were completed by several divisions within OSE as well as the Division of Psychiatry products in OND.

The conclusion of the primary clinical review by Dr. Chiang, as well as consultative reviews from the Division of Psychiatry Products, and the Division of Epidemiology from OSE recommend a Complete Response for this application. The Division of Pharmacovigilance in OSE, and the Division of Cardioresenal Products did not concur with this recommendation. Since this issue is novel and complex for psoriasis products, and is impacted by multiple behavioral and societal factors that cannot be controlled, the disparate review conclusions are understandable.

This CDTL review concludes that there is a population that would likely find brodalumab of substantial value, in certain situations, given the notable treatment effect as described above. The current recommendations from DRISK regarding the addition of a Boxed Warning and a REMS which would document informed consent by both the patient and prescriber are sufficient to mitigate the neuropsychiatric risks as currently understood.

The available information is incomplete, and was of inadequate duration to completely inform this risk. While more than 4400 subjects received at least one dose of brodalumab during development, Phase 3 trials were discontinued abruptly due to the suicide related risks, and the information typically accumulated from ongoing, long term trials which are typically still ongoing during the NDA/BLA review is notably absent. Additional information to further characterize these risks is recommended post approval even though the complexities of assessments for psychiatric events will limit any definitive conclusions. However, attempts to study this product in a post-marketing environment should be made to provide information for patients and prescribers in the best practices for brodalumab going forward.

This may be particularly important since there were no specific exclusion criteria for psychiatric disorders or substance abuse in the brodalumab program. This will also impact the evaluation of the risk/benefit for brodalumab across the therapeutic context of other approved therapies. Since there were no completed suicides during the 12 week controlled periods of the Phase 3 trials, the impact of this type of information will be inferential since no statistical or causal conclusions are possible from the data.

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The details of the multiple safety reviews across various divisions will not be repeated here due to limitations of space and time, but are summarized in Dr. Chiang's clinical review. The following issues are particularly impactful to my conclusion that differs from the primary clinical review by Dr. Chiang.

The safety data from all brodalumab clinical trials included a total of 6 completed suicides in (4 subjects with psoriasis, 1 subject with rheumatoid arthritis, and 1 subject with psoriatic arthritis). Long-term safety data related to suicidal ideation and behavior (SIB) in subjects with psoriasis are not available at this time because of the early termination of psoriasis trials by the IND Sponsor.

The four suicide events occurred at a time ranging from approximately 13 to 120 weeks after the subjects began their brodalumab treatment at 210 mg dose and at 14-58 days after the subjects received their last 210 mg dose of brodalumab.

Dr. Chiang's review concludes, "The safety signal in the brodalumab clinical programs cannot be ignored. In order to adequately ascertain the risk, a randomized clinical trial with one or two active controls, in the same psoriasis population, should be considered prior to approval. If the applicant seeks to have the product indicated for second line treatment, a RCT should be designed to evaluate second line therapy for brodalumab. The risk of SIB cannot be remediated simply by making this product a second line treatment. Psoriasis patients are already at an increased risk for psychiatric co-morbidities and this reviewer does not believe further exposure to the brodalumab product is appropriate."

Dr. Andrew Mosholder, from the Division of Epidemiology in OSE, provided the following analyses of suicide related events across various product experiences to data. Multiple limitations affect the interpretation of this data, particularly again with cross study comparisons and the sensitivity of assessments for related neuropsychiatric events. Nonetheless, Dr. Mosholder's conclusion that "Comparisons to development programs for other psoriasis products, biologics and one small molecule, indicate an inordinate number of completed suicides in brodalumab clinical trials" appears to be generally substantiated by the available data.

| 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** | 18 | 57.5 | 172.5 | 229.9 | 24 | 229.9 |
| Brodalumab, Ps trials (from 120d SU) | 4,464 | 9162 | 4** | 15 | 43.7 | 163.7 | 207.4 | 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 | 1 | 2 | 67.4 | 134.9 | 202.3 | 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 | 9† | 0 | 140 | 140 | 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 |

*One subject committed suicide during screening **Includes suicides during post-treatment follow-up †10 cases were found by DDDP reviewer ‡Adjudicated with C-CASA PY patient-years, Ps psoriasis, PsA psoriatic arthritis, RA rheumatoid arthritis

His review also notes that “Data on psychiatric adverse events other than SIB do not suggest a relationship to brodalumab, but detection of adverse mental effects in the trials was probably limited.”

Dr. Jean Kim's review from the DPP in OND concludes, "Based on the review of the pooled data from the 12-week placebo-controlled induction phase of the three Phase 3 psoriasis trials for brodalumab, no statistically significant association of SIB elevation was found for brodalumab versus placebo. However, the generalizability of this finding is limited by the relatively short duration of the study period, the overall rare incidence of SIB events, and the use of different scales and adjudication methods during different phases of the clinical trials to detect and classify SIB events (although the same method was used at least during the 12-week induction phase alone.) Also, the C-CASA method used during the induction phase is intuitively considered less sensitive at detecting SIB events than the eCSSRS."

DPP noted the inability to establish causality to brodalumab and recommended a Complete Response and proposed "that the sponsor conduct an active-controlled, parallel group study with brodalumab focusing on frequent monitoring for psychiatric symptoms, especially suicidal ideation and behavior but also depressive symptoms. The active control agent should be a psoriasis agent which appears to have low risk for SIB events. This may permit better understanding of the relationship between brodalumab treatment and SIB as well as determination of risk factors for SIB, which might inform a future REMS. It is further recommended that this study be conducted prior to approval, because of the current availability of safe and effective agents to treat psoriasis and the potential for fatal and other serious sequelae of suicidal behavior that might be produced by brodalumab treatment if a true causal relationship exists."

Dr. Robert Levin, from the Department of Pharmacovigilance in OSE, did not conclude that a Complete Response was warranted. His review points out that "These populations have a highly elevated risk of psychiatric disorders and symptoms, including SIB." The applicant makes the same argument. He further concludes, "The pattern of neuropsychiatric events reported in the uncontrolled phases was similar to that in the controlled phase, with the exception of completed suicide. Information about the cases of completed suicides was quite limited, and it is extremely challenging to assess the potential relationship between brodalumab treatment and the completed suicides."

I find the argument that these observed suicide events could be explained by the overall background rate of psychiatric disorders in the psoriasis population, or by the gradual increase in general population suicide rates over the past few decades specious. As noted in Dr. Mosholder's data above, the number of suicides observed in the truncated brodalumab program exceeds the number of suicides noted in all other systemic psoriasis products put together. Though the TNF blocker programs date back 15 years ago, several of these programs, including the recently approved secukinumab and ixekizumab, transpired over the last five years. Dr. Levin's conclusion regarding lack of establishment of causality, however is, of course, accurate due to the limitations of the both the drug exposures and the sensitivity of psychiatric assessments which were conducted, most of which occurred following identification of the suicide related risks.

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The applicant's primary contention regarding this neuropsychiatric data is that a causal relationship is not conclusively demonstrated, and that a biologic mechanism related to downstream cytokine effects is unlikely. They have also presented analyses based on exposures per patient years, which tends to dilute the impact of these rare events.

No Agency review, including this one, contends that causality for these events has been demonstrated. Not only is the data insufficient, but the Phase 3 trials were abruptly discontinued before completion due to concerns that they were not safe to proceed. However, this review concurs that causality is not the standard for either Boxed Warnings, or REMS, or REMS with ETASU.

The applicant proposes a risk management plan, which proposes to identify the suicides and suicidal behaviors in the Warnings and Precautions section of labeling, a Communication Plan, enhanced pharmacovigilance, and participation in the Corrona psoriasis registry. This reviewer concurs with the assessment that this would be very inadequate given the extent of fatal events observed during brodalumab treatment.

In consideration of the risk/benefit determination for this application, it is again noted that no psoriasis product is universally successful, or curative for treatment of plaque psoriasis. As noted above, treatment effects for typical psoriasis outcomes, including clearance of disease and quality of life measures, are substantial for brodalumab treatment, and there are patients who deserve this option, even with the risk of an uncommon fatal outcome. With adequate informed consent, and appropriate follow-up and clinical monitoring, there is likely a subset of prescribers and psoriasis patients who would find this risk/benefit acceptable. This review recommends allowing brodalumab to be marketed with labeling that would include a Boxed Warning, full statement of risks, and a REMS with ETASU to insure that patients and prescribers appreciate the risks and can take appropriate clinical monitoring to mitigate the risk of suicide related events. A post marketing trial to further assess the risks should also be required so that the inadequacies of the information in this application due to the truncated phase 3 development can be supplemented with prospective assessments.

9. Advisory Committee Meeting

As discussed above, the safety issue of suicide/suicidal behavior is critical to the risk/benefit determination and was the focus of the Advisory Committee discussion.

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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 brodalumab application.

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 on 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 majority of the panel voted 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, but only if certain risk management options for SIB beyond labeling are implemented. Of those who voted for “B”, the majority stated that they supported a registry of some type. Two committee members recommended a black box warning.

10. Pediatrics

This product triggers PREA as a new active ingredient.

The PeRC first met to discuss the Pediatric Study Plan (PSP) and waiver/deferral proposal on January 14, 2015, and concurred with the Division recommendation.

The PSP included a recommending a partial waiver for studies in pediatric patients less than 6 years of age and a determination that pediatric studies in population 6-17 years of age with moderate to severe psoriasis should be deferred at least until after adult studies have been completed and a determination of safety and efficacy has been made for adult psoriasis subjects.

On July 6, 2016, the PeRC met to discuss the suicide/suicidal behavior safety issues identified in the review. They noted that there have been 6 suicides in the adults using the product, which is higher than numbers of suicides for any other monoclonal antibody for psoriasis.

The PeRC agreed that studies should not be initiated in pediatric patients until the suicidality concern is clarified.

The PeRC concurred with the plan for a partial waiver in patients less than 6 years of age because studies are impossible and highly impractical and to consider waiver/deferral of studies in older patients after the AC discussion. As this issue remains unresolved, the deferral for ages 6-17 will be recommended until adequate adult, post marketing data is sufficient to allow pediatric trials to be initiated. The currently proposed timetable goal is for 2022.

11. Other Relevant Regulatory Issues

No issues related to financial disclosures, GCP issues, or patent issues were identified in the review of the application.

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GMP inspections are complete, and there are no outstanding issues impacting approval from the Office of Compliance. The Office of Compliance has made an overall “Acceptable” recommendation for the facilities involved in this NDA.

The Office of Scientific Investigators (OSI) was consulted to review the conduct of both clinical trials, and included the inspections as noted by Dr. Blay in his OSI review:

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

There are no outstanding regulatory issues that will impact the approval of this application.

12. Labeling

The trade name of “Siliq” has been determined to be conditionally acceptable by Office of Medication Error Prevention and Risk Management on March 16, 2016.

Prescribing Information

Review of the proposed label submitted by the applicant was based on evaluation of the clinical trials for the BLA as well as DMEPA, DRISK, and OPDP consultative reviews.

This CDTL reviewer concurs with the review team conclusion that labeling, particularly as proposed by the applicant, is not adequate by itself to communicate necessary safety information to prescribers. A REMS with ETASU is warranted to assure safe use and is discussed below.

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While there are no disagreements from the review team that adequate evidence of efficacy of brodalumab at the proposed dose for the moderate to severe psoriasis population has been presented, the applicant's proposed labeling underplays the potential significance of the completed suicides and disparate findings in analyses of suicidal ideation and behavior. Their argument asserts that there is no evidence of causality for these events. Their proposed labeling did not include a boxed warning, and their risk mitigation concentrated on a communication plan to inform prescribers.

In the opinion of this reviewer, the events of completed suicide and suicidal behaviors clearly merit a boxed warning and meet the elements described in the guidance *Warnings and Precautions, Contraindications, and Boxed Warning Sections of Labeling for Human Prescription Drug and Biological Products*.

Since both my recommendation, as well as that from senior management, have determined that a REMS with ETASU is necessary for the safe use of this product, a boxed warning is appropriate as described in the guidance:

“FDA approved the drug with restrictions to ensure safe use because FDA concluded that the drug can be safely used only if distribution or use is restricted (e.g., 21 CFR 314.520 and 601.42 “Approval with restrictions to assure safe use” or under 505-1 (f)(3) of the Federal Food, Drug, and Cosmetic Act (FDCA) Risk Evaluation and Mitigation Strategies” Elements to assure safe use).”

Even if a REMS were deemed unnecessary, the following element from the Boxed Warning section of the guidance cannot be disputed:

“There is an adverse reaction so serious in proportion to the potential benefit from the drug (e.g., a fatal, life-threatening or permanently disabling adverse reaction) that it is essential that it be considered in assessing the risks and benefits of using the drug.”

Additional information will be included in the Warnings and Precautions section to labeling to provide further detail and context for the observed events. The disagreements related to patient labeling (i.e., Medication Guide, Patient Information, Instructions for Use), and carton and container labeling appear to be minor and easily resolvable during the ongoing labeling negotiation process.

Final agreement on Agency proposed labeling, including carton/container labeling, is pending as of the due date of this CDTL review. At this time, the applicant has not accepted the recommendations for a Boxed Warning and REMS with ETASU, and the applicant has

not submitted a revised labeling proposal which incorporated these Agency recommendations. The details of the agreed upon labeling will be attached to the action letter assuming eventual agreement by the applicant.

13. Postmarketing Recommendations

Risk Evaluation and Management Strategies (REMS)

Following the Advisory Committee discussion, several internal meetings were held to determine the optimal regulatory path forward for this application, and included presentations before the REMS Oversight Committee. The conclusion of those discussions determined that the product could be approved for marketing, but only if labeling were optimized to inform the safety risks, and include a REMS with ETASU to assure that both prescribers and patients would be adequately informed of the risks involved.

- Optimized labeling would include:
 - A Boxed Warning discussing the potential increased risk of suicidality with brodalumab
 - A Limitation of Use that the brodalumab should only be used in patients who have failed to respond, or lost response, to other biologic therapies
 - A recommendation to discontinue therapy in patients who do not achieve an adequate response within 12 weeks
- The REMS with ETASU (elements to assure safe use) would include:
 - Physician certification: A ‘streamlined’ process by which physicians learn of the risk of suicidality, acknowledge their understanding of the risk, and agree to counsel patients on the risk.
 - Pharmacy certification: To ensure that brodalumab prescribers are certified.
 - Safe use conditions: Patients will need to sign an acknowledgement form asserting that they were counseled by their physician on the potential risk of suicidality, and that they understand that this is a potential risk associated with brodalumab treatment.

Cross Discipline Team Leader Review

As of the date of this review, the applicant has not submitted a response or timetable for submission of assessments of a REMS, and/or an implementation system.

Postmarketing Requirements (PMRs) and Commitments (PMCs)

There will be a PREA PMR to address the pediatric population from age 6-17, with studies deferred until 2022.

The recommended post-marketing studies to be conducted are recommended from the product quality review. None of these issues are approvability issues and these can be conducted post-approval.

(b) (5)

Cross Discipline Team Leader Review

No PMC/PMR recommendations were proposed by the nonclinical and clinical pharmacology reviews.

14. Recommended Comments to the Applicant

As of the PDUFA timeline due date of this CDTL review, labeling and REMS negotiations with the applicant have not been completed. In fact, despite several recent teleconferences with the applicant, no submission of optimized labeling to include a Boxed Warning, or REMS timeline, has been received and the applicant has made no submissions at all for the past two weeks, despite the upcoming action date of November 16, 2016. A final action decision, and review of REMS proposals, is pending completion of these discussions.

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/s/

DAVID L KETTL
09/16/2016