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APPLICATION NUMBER:

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MEDICAL REVIEW(S)

Clinical Review
 Gary T Chiang MD, MPH
 BLA 761032
 SILIQ® (Brodalumab)

CLINICAL REVIEW

Application Type	Biologic Licensing Application
Application Number(s)	761032
Priority or Standard	Standard
Submit Date(s)	16-NOV-2015
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Division/Office	DDDP/ODE3/OND
Reviewer Name(s)	Gary T Chiang MD, MPH
Review Completion Date	25-AUG-2016
Established Name	Brodalumab
(Proposed) Trade Name	SILIQ®
Applicant	Valeant Pharmaceuticals
Formulation(s)	Single use prefilled syringe: 210 mg of brodalumab in 1.5mL solution (140mg/mL)
Dosing Regimen	210 mg SC injection at Weeks 0, 1, and 2 followed by 210 mg Q2W
Applicant Proposed Indication(s)/Population(s)	For the treatment of adult patients with moderate to severe plaque psoriasis who are candidates for systemic therapy or phototherapy
Recommendation on Regulatory Action	Complete Response (CR)
Recommended Indication(s)/Population(s) (if applicable)	For the treatment of adult patients with moderate to severe plaque psoriasis who are candidates for systemic therapy or phototherapy

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Glossary

AC	advisory committee
AE	adverse event
AMG	AMGEN Inc.
BLA	biologics license application
BPCA	Best Pharmaceuticals for Children Act
BRF	Benefit Risk Framework
BW	Body weight
CBER	Center for Biologics Evaluation and Research
CDER	Center for Drug Evaluation and Research
CDRH	Center for Devices and Radiological Health
CDTL	Cross-Discipline Team Leader
CEC	Cardiac Evaluation Committee
CFR	Code of Federal Regulations
CMC	chemistry, manufacturing, and controls
COSTART	Coding Symbols for Thesaurus of Adverse Reaction Terms
CRF	case report form
CRO	contract research organization
CRT	clinical review template
CSR	clinical study report
CS	completed suicide
CSS	Controlled Substance Staff
CSSRS	Columbia Suicide Severity Rating Scale
DCRP	Division of Cardiac and Renal Products
DEPI	Division of Epidemiology
DODAC	Dermatology and Ophthalmology Drugs Advisory Committee
DPP	Division of Psychiatry Products
DPV	Division of Pharmacovigilance
DMC	data monitoring committee
ECG	electrocardiogram
eCTD	electronic common technical document
ETASU	elements to assure safe use
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act of 2007
FDASIA	Food and Drug Administration Safety and Innovation Act
GCP	good clinical practice
GRMP	good review management practice

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HADS	Hospital Anxiety Depression Scale
ICH	International Conference on Harmonization
IND	Investigational New Drug
ISE	integrated summary of effectiveness
ISS	integrated summary of safety
ITT	intent to treat
MACE	Major Adverse Cardiac Event
MedDRA	Medical Dictionary for Regulatory Activities
mITT	modified intent to treat
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Event
NDA	new drug application
NME	new molecular entity
OCS	Office of Computational Science
OPQ	Office of Pharmaceutical Quality
OSE	Office of Surveillance and Epidemiology
OSI	Office of Scientific Investigation
PD	pharmacodynamics
PHQ-8	Personal Health Questionnaire Depression Scale - 8
PI	prescribing information
PK	pharmacokinetics
PMC	postmarketing commitment
PMR	postmarketing requirement
PP	per protocol
PPI	patient package insert
PREA	Pediatric Research Equity Act
PRO	patient reported outcome
PSUR	Periodic Safety Update report
RCT	Randomized control trial
REMS	risk evaluation and mitigation strategy
SAE	serious adverse event
SAP	statistical analysis plan
SGE	special government employee
SIB	suicide ideation and behavior
SOC	standard of care
TEAE	treatment emergent adverse event

1 Executive Summary

1.1. Product Introduction

Valeant Pharmaceuticals is developing brodalumab (previously AMG-827), a human monoclonal immunoglobulin G2 (IgG2) which binds to human interleukin-17 receptor A (IL-17RA) and blocks the biological activities of IL-17A, IL-17C, IL-17F, IL-17A/F heterodimer and IL-25. The IgG2 antibody is expressed in a CHO cell line that is a heterotetramer consisting of 2 heavy chains of the IgG2 subclass and 2 light chains of the kappa subclass that are covalently linked through disulfide bonds.

Figure 1: Brodalumab Binds IL-17RA and Blocks Biological Activity of Multiple IL-17 Family Cytokines

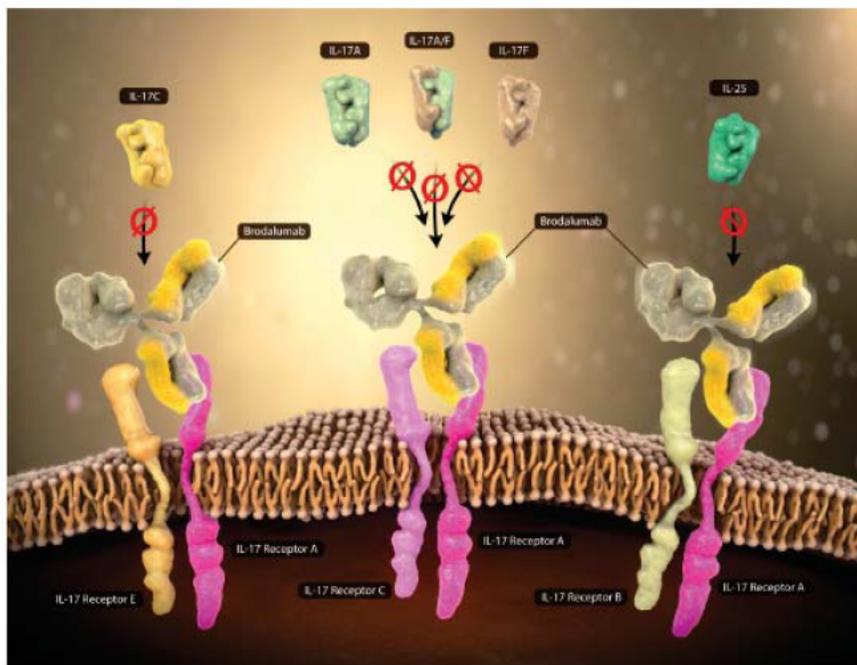


Figure: Adopted from Applicant's submission

The clinical development program includes data from three Phase 3 clinical trials in subjects with moderate to severe chronic plaque psoriasis. Approximately 3207 subjects have over 12 months of exposure to brodalumab. The presentation proposed is a prefilled syringe for subcutaneous administration at 210 mg (140 mg/mL, 1.5 mL PFS) at weeks 0, 1, and 2 followed by biweekly administration.

1.2. Conclusions on the Substantial Evidence of Effectiveness

Valeant Pharmaceuticals submitted a BLA for brodalumab (SILIQ) to be administered by PFS at 1.5mL (140mg/mL) to a dose of 210mg at 0, 1, and 2 weeks with subsequent maintenance of Q2W, for the treatment of moderate to severe plaque psoriasis in adults who are candidates for systemic therapy or phototherapy.

The applicant submitted three Phase 3 clinical trials and a single Phase 2 clinical trial for the determination of safety and efficacy of brodalumab in psoriasis subjects. The development program also included sufficient CMC, pharmacology/toxicology, and clinical pharmacology evidence to support marketing of the biologic product.

The efficacy of brodalumab for the treatment of psoriasis was supported by the three pivotal Phase 3 clinical trials (Studies 20120102, 20120103, 20120104) with Trials 03 and 04 that also included an ustekinumab arm as an active comparator. All trials enrolled subjects 18 years 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 a 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. For all trials, both brodalumab doses were superior to placebo ($p < 0.001$) for the co-primary (PASI 75 and sPGA of 0 or 1 at Week 12) as well as the secondary endpoints (PASI 100, sPGA of 0, and Psoriasis Symptom Inventory (PSI) responder at Week 12). For the comparison of brodalumab against ustekinumab, brodalumab 210 mg dose was superior to ustekinumab ($p < 0.001$) for the primary endpoint of PASI 100 at Week 12.

The safety review of brodalumab presented challenges. Late into the clinical studies, a suicide signal emerged with 4 completed suicides in the Phase 3 clinical trials. A total of 6 completed suicides in all brodalumab clinical trials were discovered (4 in psoriasis, 1 in rheumatoid arthritis, and 1 in psoriatic arthritis). A total of 34 subjects had 39 Suicidal Ideation and Behavioral (SIB) events (SIB is defined as completed suicides, suicidal ideation, and suicidal behaviors). The Phase 3 clinical trials were then terminated by Amgen, the sponsor at that time, leading to an absence of long-term and ongoing data to inform safety. Evaluation of the remaining data suggests a possible drug association with SIB, although the lack of definitive causation for these rare events persists.

In addition to the SIB safety issues, the action of brodalumab theoretically affects cardiovascular outcomes and major cardiovascular adverse events. The review of the safety data available for rare and long-term cardiovascular events was also truncated due to termination of all studies in brodalumab. The review of available cardiac safety data suggests possible association of IL-17 receptor inhibition to increase cytokine inflammation leading to worsening MACE. Cardiology consultation with the Division of Cardiology and Renal Product

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suggested a lack of direct association of brodalumab to MACE due to a paucity of data. And a review of the available literature is unclear for the mechanistic action of brodalumab causing worsening of atherosclerosis.

In summary, this new biologic entity for the treatment of chronic plaque psoriasis has a mechanism of action blocking the IL-17A receptor in the cytokine cascade. The biologic effects of the increase in IL-17A and its interaction with other cytokines are not well understood; however, evidence does suggest that interactions with inflammatory changes in the central nervous system and cardiovascular atherosclerosis exist. This reviewer believes the regulatory standard for safety has not been met, referring to 21 CFR 314.125 (b)(4), "There is insufficient information about the drug to determine whether the product is safe for use under the conditions prescribed, recommended, or suggested in its proposed labeling."

The safety signal for rare psychiatric adverse events in subjects treated with brodalumab is concerning. The data collected for ascertaining any neuropsychiatric adverse event in the conducted clinical trials are deficient. In order to fully assess the risk of SIB, this reviewer recommends a pre-approval randomized-controlled clinical trial (RCT) with active comparators and a full ascertainment of neuropsychiatric adverse events prospectively to evaluate the risk of SIB in brodalumab treated subjects (details of proposed RCT in REMS section of this review). In addition to the SIB evaluation, the RCT should review MACE in these subjects to estimate the risk of cardiac adverse events in the investigational drug product and the active comparator. I believe this is the only approach that will alleviate the uncertainties in the safety profile of the brodalumab drug product.

My conclusion notwithstanding, the Dermatology and Ophthalmology Drugs Advisory Committee (DODAC) voted unanimously to approve brodalumab 210 mg for the treatment of moderate to severe psoriasis. If approved, this reviewer recommends a boxed warning with appropriate Section 5: Warnings and Precautions labeling to adequately convey the risks and appropriate Risk Mitigation Strategies (REM). In addition, a post marketing requirement (PMR) for a RCT with active comparator arm(s) would be required to fully ascertain the SIB risks.

1.3. Benefit-Risk Assessment

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Benefit-Risk Summary and Assessment

Chronic plaque psoriasis is a common, inflammatory, multi-system disease with both psychological and physical burden affecting 1-2% of the U.S. population. Brodalumab is a new biologic product with a novel mechanism that blocks the IL-17A receptors. The clinical studies show that brodalumab is effective in treating psoriasis and met its primary endpoints of PASI-75 and sPGA of clear (0) or almost clear (1). Two of the Phase 3 clinical trials also showed that brodalumab was more effective than ustekinumab in direct head to head comparison with the endpoint of PASI-100 (completely clear skin). The safety review of brodalumab presented significant findings. Late into the clinical studies, the suicide signal emerged with 4 completed suicides in the Phase 3 clinical trials. A total of 6 completed suicides in all brodalumab clinical trials were identified (4 in psoriasis, 1 in rheumatoid arthritis, and 1 in psoriatic arthritis). However, one of the completed suicides was later determined as a possible overdose and not suicide as ruled by the medical examiner. The Phase 3 clinical trials were terminated early by the sponsor, leading to a lack of long-term and ongoing data to assure safety. Evaluation of the remaining data suggests a possible drug association with suicide ideation and behavior (SIB), although the lack of definitive causation persists. In addition to the SIB safety issues, the actions of brodalumab theoretically affect cardiovascular outcomes and major cardiovascular adverse events. The review of the safety data available for rare and long-term cardiovascular events was also truncated due to termination of all studies in brodalumab. The review of available cardiac safety data suggests possible association of IL-17 receptor inhibition to increase cytokine inflammation leading to worsening MACE. Cardiology consultation with the Division of Cardiology and Renal Product suggested a lack of direct association of brodalumab to MACE due to lack of data. And a review of the available literature is unclear for the mechanistic action of brodalumab causing worsening of atherosclerosis. In the opinion of this reviewer, psoriasis, although a serious disease, is not a fatal disease and the risk of SIB and the possible association with MACE is a safety hurdle with an unfavorable risk/benefit analysis for psoriasis patients.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	<ul style="list-style-type: none"> Psoriasis is a common, chronic, inflammatory, multi-system disease with predominantly skin and joint manifestations affecting approximately 2-3 % of the US population. Approximately 80% of those affected with psoriasis have mild to moderate disease, with 20% having moderate to severe psoriasis affecting more than 5% of the body surface area. Psoriasis is a disabling disease which has important social, psychological and 	Moderate to severe psoriasis is a serious and at times disabling condition that has a substantial impact on patient's lives. Safe and effective treatment has the potential to greatly improve the quality of life for a patient with moderate to severe psoriasis

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Dimension	Evidence and Uncertainties	Conclusions and Reasons
	<p>economic consequences. The impact of psoriasis on the quality of life is reported to be comparable with that observed in other chronic medical conditions such as diabetes and depression.</p> <ul style="list-style-type: none"> The National Psoriasis Foundation (NPF) conducted a survey in 2014 (811 respondents) which reported the following negative impact on the Quality of Life (QoL) in psoriasis patients: nearly 60% say psoriasis impacts their self-esteem and emotional well-being, more than two-thirds avoid social activities, including dating and intimacy and 51% of patients state that they are un- or undertreated, the top two reasons being fear of side effects and cost or perceived cost of therapy. 	
<p>Current Treatment Options</p>	<ul style="list-style-type: none"> Currently approved drugs for the treatment of moderate to severe psoriasis include the anti-metabolite methotrexate (MTX), tumor necrosis factor (TNF) inhibitors such as etanercept, adalimumab and infliximab, IL-12+23 antagonist ustekinumab, IL-17A antagonist secukinumab and ixekizumab, T cell inhibitor cyclosporine (CSA), retinoid soriatane and phosphodiesterase 4 inhibitor apremilast. Phototherapy, either PUVA (UVA light combined with the psoralen methoxsalen) or UVB light therapy (narrow or broadband) is also a standard of care treatment for moderate to severe psoriasis patients. The efficacy of these products is generally measured on the Psoriasis Area and Severity Index (PASI) with the change from baseline as the most common primary efficacy endpoint. The PASI 75 (75% reduction in the PASI score compared to baseline) for currently available drug therapies varies from highly efficacious (PASI 75 ≥ 70%) for cyclosporine, infliximab, adalimumab, ustekinumab, secukinumab and ixekizumab to moderately efficacious (PASI 75 ≥ 40%) for methotrexate and etanercept to somewhat efficacious (PASI 75 	<p>There are multiple drugs approved that have an acceptable risk-benefit profile for the treatment of moderate to severe psoriasis. All of the approved products have significant risks and there is room for both more efficacious and potentially safer products for these patients.</p>

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Dimension	Evidence and Uncertainties	Conclusions and Reasons
	<p>≥ 20%) for acitretin and apremilast¹. Phototherapy is highly efficacious as well</p> <ul style="list-style-type: none"> • Significant safety concerns for the moderately and highly efficacious approved products include immunosuppression with the associated risk for serious and in some cases opportunistic or unusual infections, cytopenias, hepatotoxicity and hypersensitivity events. See Table 1 for specifics for each product. 	
<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 (02, 03, and 04); Trials 03 and 04 included an ustekinumab comparator arm. • The 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 ≥10% at baseline. Brodalumab-treated subjects received a loading dose weekly for the first 2 weeks and Q2W thereafter. • 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., ≥75% reduction in PASI score) and an sPGA of 0 or 1. Secondary endpoints were PASI 100 (i.e., 100% reduction in PASI score), sPGA score of 0, and Psoriasis Symptom Inventory (PSI) responder (i.e., total score ≤ 8, with no 	<p>The evidence submitted by the applicant to support the approval of brodalumab has met the statutory evidentiary standard for providing substantial evidence of effectiveness under the proposed conditions of use. The trials were adequate and well-controlled. For the induction dose proposed for marketing (brodalumab 210 mg at 0, 1, and 2 weeks then Q2W) the proportion of responders for a sPGA of 0 or 1 were 76%, 79% and 80% and the proportion of PASI 75 responders were 83%, 86% and 85% respectively for trials 02, 03, and 04. The improvement seen with treatment with brodalumab places this product in the “highly efficacious” category and is highly clinically meaningful.</p>

¹ The efficacy grading system used is for cross study comparison, and is not published.

² Henry W. Lim, MD et al. Phototherapy in dermatology: A call for action. JAAD. Vol # 72: 6, June 2015, Pages 1078–1080

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Dimension	Evidence and Uncertainties	Conclusions and Reasons
	<p>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).</p> <ul style="list-style-type: none"> • 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 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>Risk</p>	<ul style="list-style-type: none"> • The safety database for brodalumab includes all patients from the three pivotal Phase 3 clinical trials for psoriasis and supportive data from 2 additional clinical trials in rheumatoid arthritis and psoriatic arthritis. The drug exposure is considered less than adequate due to the early termination of all clinical trials by the sponsor. • Brodalumab is an IL-17RA (receptor antagonist) with a mechanism of action on other cytokines, effects on neuropsychiatric behavior, and cardiovascular atherosclerosis that is unclear. • Limited controlled data for uncommon events and truncated long-term safety trials presents a challenging benefit to risk analysis. • In addition to the SIB and MACE safety issues, the drugs affecting cytokines in the cascade presents a safety profile of neutropenia, increased infections, increase fungal infections, worsening of 	<p>Due to the mechanistic actions of this novel IL-17 receptor antagonist, theoretical issues affecting the safety of this product in central nervous system and cardiovascular atherosclerosis has been suggested. Although the safety profile is consistent with other systemic agents used for the treatment of psoriasis, the findings of ambiguous safety signal in SIB and MACE presents challenging risk/benefit analysis.</p>

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Dimension	Evidence and Uncertainties	Conclusions and Reasons
	inflammatory bowel disease, immunosuppression, and hypersensitivity events.	
Risk Management	<ul style="list-style-type: none"> • The benefits and risk of this product is not balanced. Safety signals for both SIB and MACE limits the use of this drug in an already vulnerable population with increased psychiatric co-morbidities and cardiovascular risks. • In addition to the safety signals, the safety profile of biologics have to be considered including; increased infections, immune suppression, neutropenia, and association with risk for serious opportunistic infections. 	In this reviewer’s judgment, the risk outweighs the benefits provided by this biologic. The safety signal for SIB requires further data to remediate the risk in this high co-morbid population. It is recommended that a Complete Response (CR) be issued to the applicant.

2 Therapeutic Context

2.1. Analysis of Condition

Psoriasis is a common chronic skin disorder affecting over 7.5 million patients in the United States, most commonly characterized by well-demarcated erythematous plaques with silver scales. Chronic plaque psoriasis is the most common variant of psoriasis. 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.

2.2. Analysis of Current Treatment Options

For PsO, the available approved systemic treatments for disease that is moderate to severe in candidates for systemic therapy or phototherapy is described in the tables below. While multiple topical therapies are available, and may be used in combination with systemic treatments, 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	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		
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

Source: Table reconstructed from recent review of literature.

Phototherapy

This therapy involves exposures to UVB (including narrowband) or to UVA in combination with the photosensitizer, Psoralen, a photochemotherapy that goes by the acronym PUVA. Phototherapy requires frequent office visits (e.g. three times per week) and carries an increased risk of squamous cell carcinoma (of the skin).

Table 2: Comparative Response Rates for Psoriasis Biologics

	Etanercept (Enbrel®)	Infliximab (Remicade®)	Adalimumab (Humira®)	Ustekinumab (Stelara®)	Ixekizumab (Taltz®)	Secukinumab (Cosentyx®) ^b	Brodalumab (Siliq®)
PASI 75	47%	79%	72%	72%	89%	78%	85%
PASI 100	NA	NA	NA	NA	37%	NA	41%
sPGA 0/1	51% ^a	85% ^a	63% ^a	68% ^a	82%	63% ^a	79%

Source: Clinical Review of Data from PI.

^a sPGA clear (0) or minimal (1)

^b Secukinumab only included PASI 90 (56%)

In the above table, comparative response rates are shown for the biologics available on the market for treatment of moderate to severe adult psoriasis. Note that ixekizumab and secukinumab are IL17A antibodies. The mechanism of action for brodalumab, which bind to the receptor rather than the cytokine, makes that product unique.

3 Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

Brodalumab is not marketed in the United States or in any other countries. The applicant made the Agency aware that on July 4, 2016, the Japanese Authority approved brodalumab 210 mg for the indication of moderate to severe plaque psoriasis in adults at the FDA Advisory

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Committee meeting on 19-JUL-2016.

3.2. Summary of Presubmission/Submission Regulatory Activity

The product originated from AMGEN (AMG-827) with co-development from AstraZeneca. AMGEN manufactured and distributed the biologic for developing clinical trials. The sponsor's development program was evaluated by the Agency in early Pre-IND meetings and Phase 3 clinical protocol evaluation. The Agency made recommendations on endpoints and gave advised on development plans. The Division of Dermatology and Dental products clinical reviewer monitored safety information as the sponsor made them available. This sequence of events describes the regulatory activity related to psychiatric safety issues during drug development:

March 30, 2013: The Agency was informed of the first suicide reported in a patient taking brodalumab.

February 7, 2014: Amgen submitted a report for potential risk of Suicidal Ideation and Behavior (SIB) including a total of 3 completed suicides.

March 26, 2014: A teleconference between Amgen and the Agency took place to discuss Amgen's action plan (e.g. details of the plan, timeline, and actions already taken) in response to the SIB reported.

May 13, 2015: The Agency met with the Amgen to discuss the completed suicides and SIB observed in the clinical development program for brodalumab. There was a recommendation the Sponsor further evaluate this risk and propose a robust risk mitigation program to minimize this safety concern at the time of BLA submission.

May 29, 2015: Amgen announced they are no longer co-developing brodalumab and initiated plan for early termination of all ongoing clinical trials across all indications.

November 16, 2016: AstraZeneca submitted BLA 761032 for brodalumab for the treatment of moderate to severe plaque psoriasis in adult patients who are candidates for systemic therapy or phototherapy. The submission contained a Med Guide and CP REMS.

April 1, 2016: AstraZeneca informed the Agency that it will be transferring all rights and ownership to Valeant Pharmaceuticals North America LLC.

April 20, 2016: Mid-Cycle meeting with Sponsor during which the Agency communicated that the risk of SIB was still under review.

3.3. Foreign Regulatory Actions and Marketing History

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The applicant has submitted an EMA application for brodalumab for the treatment of moderate to severe plaque psoriasis in adults 18 years and older. As previously mentioned, the applicant made the Agency aware, at the AC meeting on 19-JUL-2016, that the Japanese Authority has approved brodalumab for marketing in Japan.

4 Significant Issues from Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety

4.1. Office of Scientific Investigations (OSI)

The Office of Scientific Investigations (OSI) was consulted to conduct routine applicant/monitor inspection for brodalumab. Three Phase 3 clinical trials were conducted to support a determination safety and efficacy. Of particular note, Dr. Mark Lebowohl (NY, USA) had two completed suicide in his clinical site. Dr. Jolanta Weglowska (POL) had the highest enrollment (n=77) with 95% brodalumab responders. The last inspection was with investigator Dr. Elzakowska-Bober.

The inspections were performed as a data audit for BLA 761032. At Dr. Lebowohl's site for Protocol 20120103, 57 subjects were screened and 49 subjects were enrolled. None of the subjects completed the study because the study was terminated in June of 2015 by the original sponsor, Amgen. The program was then transitioned to the current sponsor, AstraZeneca Pharmaceuticals LP. Signed informed consent was obtained from all 49 enrolled subjects prior to study entry. Source data on paper records were transcribed to a sponsor-provided, web-based electronic data capture program (Medidata Rave). Source data was compared to line listings. The records of 20 subjects were reviewed. Records reviewed included, but were not limited to, monitoring reports, financial disclosure, randomization, stratification, primary and secondary efficacy endpoints, adverse events, concomitant medications, and test article accountability. Numerous discrepancies were noted between the subject source records, the electronic Case Report Forms (eCRFs), and the line listings. In all cases, source records matched the eCRFs but these records were discrepant when compared with the line listings. The majority of the discrepancies involve the reporting of non-serious adverse events; however, in one case, an SAE (suicide) was not in the line listings. Subsequent follow up with the medical officer determined that this adverse event was reported.

In all, the conclusions to the investigations to the conduct of the clinical trials were adequate. The data generated by the sites for all clinical trials appear to be acceptable in support of the respective indication.

4.2. Product Quality

A summary of product quality assessment is provided. See full review by Agency chemist Willie Wilson, Ph.D.

Brodalumab DS is manufactured at (b) (4) using standard monoclonal antibody manufacturing processes. Brodalumab is expressed in (b) (4) Chinese hamster ovary (CHO) cells. (b) (4)

Brodalumab DP is manufactured at (b) (4) and is packaged and labeled at (b) (4). The manufacturing process for brodalumab DP is comprised of (b) (4)

The container closure system is a single-use, 2.25 mL Type 1 glass syringe with a stacked stainless steel needle, (b) (4) needle shield (b) (4) and (b) (4) plunger-stopper. Syringes are filled to 1.5 mL brodalumab drug product (140 mg/mL). The pre-filled syringes are packaged in cardboard secondary containers and stored at 2 – 8°C, protected from light.

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. It is recommended that Siliq (brodalumab) be approved for human use (under conditions specified in the package insert), provided that the following issues are sufficiently addressed prior to the Action Date. The review of these issues will be included in an Addendum to the 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.

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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) 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.
9. Tightening of or modification of the proposed potency criterion for qualification of future (b) (4) 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 L-glutamic acid, rather than USP/NF L-glutamic acid, 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.

Dr. Wilson recommends an expiry period of 12 months for brodalumab DP when stored at 2 – 8oC, protected from light. Note: Additional data to extend this recommendation may be provided.

Dr. Wilson also recommend an expiry period of (b) (4) months for brodalumab DS when stored at - (b) (4).

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The post-approval stability protocols are acceptable with the exception of the testing noted above. Updated stability data will be reported to the BLA in the Annual Report. With exceptions noted above, CMC recommends approval of the proposed release specifications for brodalumab DS and DP.

There is the potential for the following PMR/PMCs. The PMR is dependent on the final determination made by the clinical review team. The PMCs are dependent of the final responses provided by Valeant.



4.3. Clinical Microbiology

Not applicable.

4.4. Nonclinical Pharmacology/Toxicology

The non-clinical review was completed by Dr. Carmen Booker. The non-clinical reviewer is recommending the application as approvable from a pharmacology/toxicology perspective. A summary of the findings are provided here.

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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.

Drug Information

CAS Registry Number: 1174395-19-7

Generic Name: brodalumab

Code Name: AMG 827

Chemical Name: anti IL-17RA monoclonal antibody

Molecular Formula/Molecular Weight: (b) (4)

Biochemical Description: Brodalumab is an IgG2 human monoclonal antibody consisting of 2 heavy chains and 2 light chains of the kappa subclass. Each heavy chain contains an N-linked glycan at a consensus glycosylation site on asparagine 292. (b) (4)

Pharmacologic Class: IL-17 receptor A antagonist, monoclonal antibody

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Figure 2: Schematic of Brodalumab Structure



Labeling review is on-going with the applicant. The non-clinical team does not recommend any PMC/PMR at this time.

4.5. Clinical Pharmacology

The Office of Clinical Pharmacology has recommended that from their standpoint, the BLA is acceptable to support the approval of SILIQ (brodalumab) for the treatment of moderate to severe plaque psoriasis in adult patients.

4.5.1. Mechanism of Action

Mechanism of action (MOA): Brodalumab is a human monoclonal Ig2κ antibody that binds to interleukin-17 receptor A (IL-17RA). 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. Because IL-17RA is a component of the heterodimer receptor for several cytokines, brodalumab inhibits the biological activities of IL-17A, IL-17F, IL-17A/F heterodimer, IL-25 (also known as IL-17E), and IL-17C.

4.5.2. Pharmacodynamics

Brodalumab increased serum IL-17A levels: Serum levels of IL-17A were increased in subjects with moderate to severe plaque psoriasis after receiving 140 mg or 210 mg brodalumab treatment compared to the pre-treatment levels. The increase in serum IL-17A level appeared to be brodalumab dose-dependent: the higher dose of brodalumab was associated with greater increase in serum levels of IL-17A.

In Phase 3 Study 02, pre-dose serum IL-17A concentrations were measured at baseline, Week 12, Week 24 and Week 48 in a subgroup of subjects. The results showed that median serum IL-17A concentrations were increased from 0.37 pg/mL at baseline to 0.76-0.92 pg/mL across different time-points following brodalumab 140 mg Q2W treatment, representing up to 2.5-fold increase of median IL-17A levels. A greater increase of serum IL-17A levels was observed for the 210 mg dose: median serum IL-17A concentrations were increased from 0.48 pg/mL to 1.44-1.62 pg/mL for the 210 mg → 210 mg treatment group and from 0.40 pg/mL to 1.45-1.70 pg/mL for the placebo → 210 mg treatment group, representing up to 4.2-fold increase of median IL-17A levels (Figure B.2.a).

In Study 20110184, both serum brodalumab and serum IL-17A concentrations were measured at different time-points following a single brodalumab (210 mg or 140 mg SC) administration in subjects with psoriasis. The results showed that serum IL-17A levels were increased following brodalumab administration. Higher serum brodalumab concentrations were associated with higher serum IL-17A concentrations; however, the increase of serum IL-17A levels appeared to be saturable at serum brodalumab concentrations greater than approximately 4 mcg/mL (Figure B.2.b).

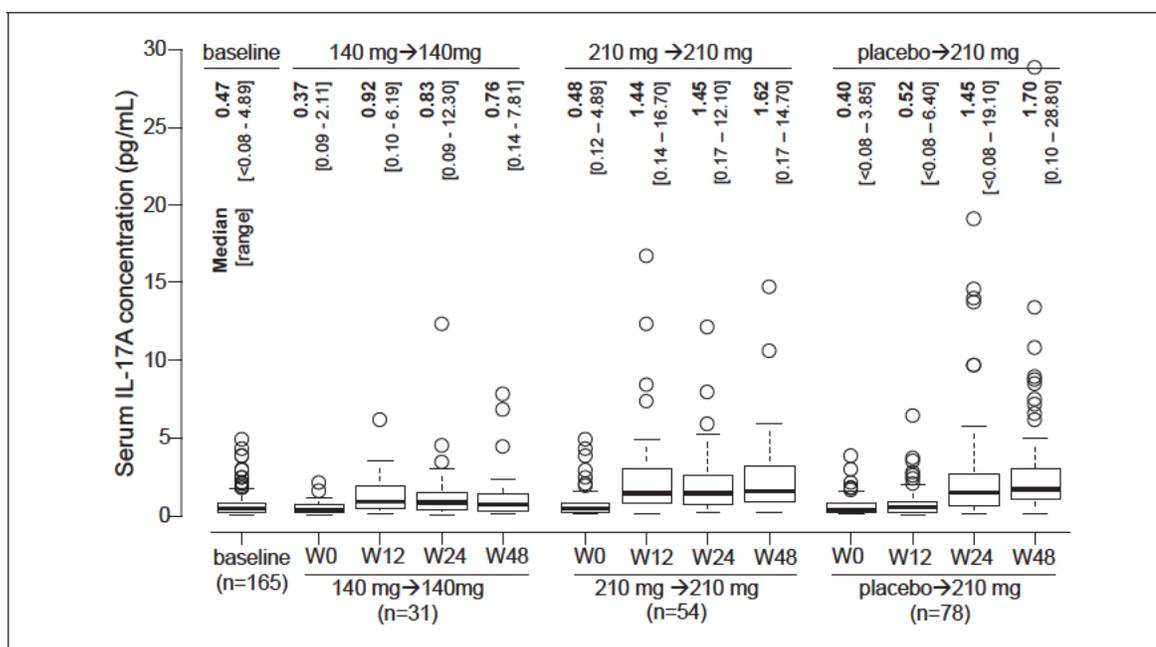


Figure B.2.a. Brodalumab increased serum IL-17A concentrations in subjects with psoriasis following 140 mg Q2W and 210 mg Q2W treatment. Pre-dose serum IL-17A concentrations were assessed at baseline, Week 12, Week 24 and Week 48 in a subgroup of subjects in Phase 3 Study 20120102. Placebo→210 mg treatment group received placebo at Week 0 and started brodalumab 210 mg treatment from Week 12. (*Data source: Reviewer’s analysis and the Applicant’s analysis presented in Table 1, MSCBCSR.20120102_IL-17A.*)

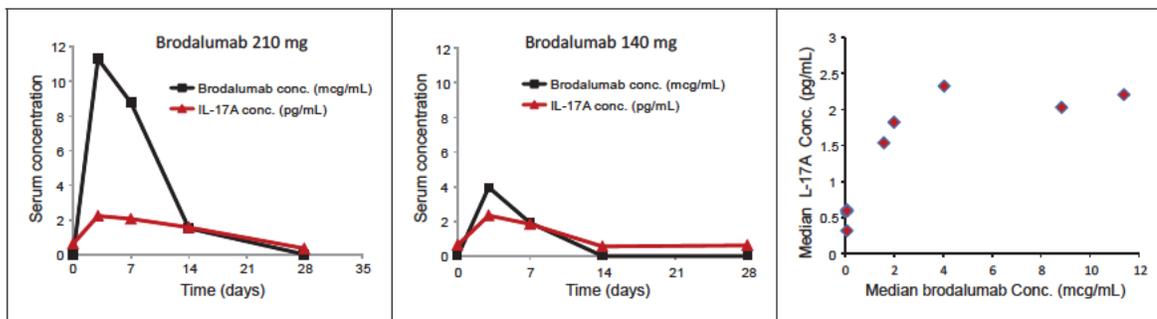


Figure B.2.b. Serum brodalumab and IL-17A concentrations in subjects with psoriasis following a single 140 mg and 210 mg treatment. Each time-point represents the median value based on 19-20 subjects in the 210 mg treatment group (left) and 9-10 subjects in the 140 mg treatment group (middle). Note the different concentration scales (mcg/mL versus pg/mL) used for plotting brodalumab and IL-17A concentrations. (*Data source: reviewer’s analysis*)

Correlation of serum IL-17A level and SIB events: Among the 165 subjects with available IL-17A serum concentration data in Study 02, three SIB events occurred in three different subjects. The data showed that these three subjects were not among these with the highest IL-17 levels (Figure B.2.c).

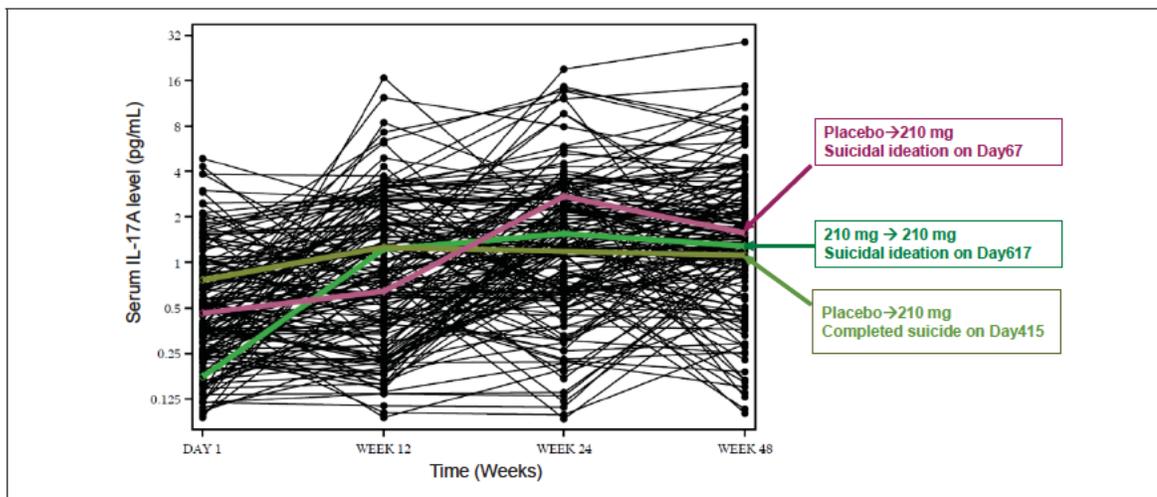


Figure B.2.c. Serum IL-17A levels in the three SIB subjects in Study 20120102. Pre-dose serum IL-17A concentrations were assessed at baseline, Week 12, Week 24 and Week 48 in a subgroup of subjects in Phase 3 Study 20120102. (*Data source: Reviewer’s analysis and plot.*)

Considerations in other cytokine levels: There is no data available to evaluate the impact of brodalumab treatment on serum levels of other cytokines in subjects with psoriasis. Theoretically, increased serum levels of IL-17A may modulate serum level of other cytokines including IL-6.

Literature reports on the potential role of cytokines in SIB: Immune dysregulation has been reported to have implications in psychiatric disorders. The literature was searched to assess the biological plausibility of brodalumab causing SIB due to cytokine modulation. The literature findings are summarized below:

- Th17 lymphocytes and IL-17 have been reported to promote blood-brain barrier disruption and central nervous system (CNS) inflammation.^{3,4} It is postulated that IL-17 could induce the production of other cytokines including IL-6 in many different cell types (e.g., astrocytes). IL-17 and IL-6 are important in CNS disorders characterized by neuroinflammation.⁵
- In a small study of RA patients, serum IL-17 levels were higher in those with anxiety (n=4) than those without (n=14). The authors concluded that IL-17 played a role in anxiety and depression in patients with RA.⁶
- In a meta-analysis of 22 studies concerning cytokines and suicidal ideation, suicide attempts or suicide completion, elevated IL-6 levels were found to be associated with suicidal ideation, suicide attempts and completed suicide.⁷ However, the authors acknowledged several limitations of the meta-analysis and indicated that larger, methodologically rigorous studies are needed to draw definitive conclusions regarding the association of inflammatory proteins and suicide.

Conclusion: The available clinical data did not show direct evidence for a correlation between brodalumab treatment-induced up-regulation of serum IL-17A levels and the SIB events observed in brodalumab psoriasis trials. As the molecular bases for SIB are unknown/complicated and the SIB events for data analysis are rare, we cannot completely rule out that brodalumab has an effect on SIB through cytokine regulation.

³ Kebir H, Kreymborg K, Ifergan I, Dodelet-Devillers A, Cayrol R, Bernard M, et al. Human TH17 lymphocytes promote blood-brain barrier disruption and central nervous system inflammation. *Nat Med*. 2007;13(10):1173-5.

⁴ Huppert J, Closhen D, Croxford A, White R, Kulig P, Pietrowski E, et al. Cellular mechanisms of IL-17-induced blood-brain barrier disruption. *FASEB J*. 2010;24(4):1023-34.

⁵ Ma X, Reynolds SL, Baker BJ, Li X, Benveniste EN, Qin H. IL-17 enhancement of the IL-6 signaling cascade in astrocytes. *J Immunol*. 2010;184(9):4898-906.

⁶ Liu Y, Ho RC, Mak A. The role of interleukin (IL)-17 in anxiety and depression of patients with rheumatoid arthritis. *Int J Rheum Dis*. 2012;15(2):183-7.

⁷ Gananca L, Oquendo MA, Tyrka AR, Cisneros-Trujillo S, Mann JJ, Sublette ME. The role of cytokines in the pathophysiology of suicidal behavior. *Psychoneuroendocrinology*. 2016;63:296-310.

4.5.3. Pharmacokinetics

Non-linear PK: Brodalumab exhibited non-linear PK with exposures that increased in a greater than dose-proportional manner and additionally the clearance of brodalumab decreased with increasing doses. Following a single subcutaneous administration, brodalumab reached peak serum concentrations (C_{max}) of 4.8±2.8 mcg/mL and 13.4±7.3 mcg/mL (mean (±SD)) for 140 and 210 mg, respectively, approximately 3 days post dose; the mean area-under-the-concentration-time curve (AUC_{0-day28})s were 27.8±20.5 mcg•day/mL and 111±64.4 mcg/mL for 140 and 210 mg, respectively; and the mean (±SD) apparent clearance (CL/F) was 14±23 L/day and 3.0±3.5 L/day for 140 and 210 mg, respectively.

Following multiple subcutaneous doses of 140 mg or 210 mg every 2 weeks (Q2W), the mean (±SD) peak serum concentrations (C_{max}) at steady-state were 7.2±6.5 mcg/mL and 20.6±14.6 mcg/mL for 140 and 210 mg, respectively. The mean (±SD) AUC_{tau} over the two week dosing interval were 81.4±77.4 mcg•day/mL and 227±167 mcg•day/mL for 140 and 210 mg, respectively.

Population PK based simulations estimate that serum brodalumab concentrations for 95% of subjects would drop below the assay quantification limit (BQL of 50 ng/mL) 32 days after discontinuation of brodalumab 140 mg Q2W treatment and 63 days after discontinuation of brodalumab 210 mg Q2W treatment.

Bioavailability: Following subcutaneous administration, brodalumab bioavailability was estimated by population PK modeling to be approximately 55%.

Intrinsic factors: Brodalumab clearance increases as body weight increases. Population PK analysis indicated that age, sex, or race did not significantly influence the PK of brodalumab.

Drug interactions: 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.

4.6. Devices and Companion Diagnostic Issues

CDRH reviewed the delivery system for brodalumab. The device constituent part of this combination product is a 2.25 mL pre-filled syringe (PFS) with a deliverable volume of 1.5 mL.

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

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

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

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

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

The deliverable volume is monitored (b) (4). The acceptance criterion is between (b) (4) mL and (b) (4) mL for the 1.5 mL PFS. This ensures that sufficient volume is dispensed to meet the label claim and minimize excess volume.

The Breakloose and extrusion ensure that the physical forces required to expel the contents of the prefilled syringe are within acceptable limits. The acceptance limit of (b) (4) N for lot release is aligned with the device verification criteria. Drug product lot release results for Breakloose and extrusion are 3 to 6 N and 5 to 13 N, respectively. This is well below the acceptance criteria of (b) (4) N. It was observed that there were no significant trends observed in the Breakloose and extrusion during stability when the drug product is stored at the recommended conditions, therefore breakloose and extrusion will not be included in the stability program.

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

4.7. Consumer Study Reviews

None

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5 Sources of Clinical Data and Review Strategy

5.1. Table of Clinical Studies

A summary of the Phase 3 clinical studies considered in the safety and efficacy evaluation of this BLA.

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Table 3: Synopsis of Clinical Trials in Safety and Efficacy Population

Trial Identity	Trial Design	Regimen/ schedule/ route	No. of patients enrolled	Treatment Duration/ Follow Up	Study Endpoints	Study Population
20120102	Phase 3, multi-center, double-blind, randomized, placebo-controlled with induction, withdrawal, retreatment, rescue, and open-label extension phases	<p>Induction: placebo or brodalumab 140 or 210 mg SC Q2W + week 1 (day 1 to week 10) [0.5 mL and 1 mL PFS]</p> <p>Withdrawal: assigned to brodalumab 210 mg SC Q2W (weeks 12 to 266) or rerandomized to placebo or brodalumab 140 mg or 210 mg SC Q2W + week 13 (weeks 12 to 266 or inadequate response)</p> <p>Retreatment: 3 doses QW of brodalumab 140 or 210 mg (day 1 to week 2 of retreatment) or brodalumab 140 or 210 mg (day 1 and week 2 of retreatment) + placebo + brodalumab 140 or 210 mg Q2W thereafter (through week 266 or inadequate response)</p> <p>Rescue (through week 52): brodalumab 210 mg SC Q2W</p> <p>OLE: Brodalumab 140 or 210 mg SC Q2W (weeks 52 to 266 or inadequate</p>	<p>661/633</p> <p>628/415</p> <p>149/106</p> <p>36/35</p>	<p>Total: 266 weeks</p> <p>Primary analysis: 52 weeks</p>	<p>PASI75, sPGA</p> <p>BSA, PSSI, SSA, NAPSI, PROs</p>	<p>Subjects with stable moderate to severe plaque psoriasis for ≥ 6 months</p> <p>Biologic therapy candidate BSA involvement ≥ 10% PASI score ≥12 sPGA ≥ 3</p> <p>Age 18 to 75 years</p>

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		Excluding subjects who were still on ustekinumab at week 52, 677 subjects enrolled at sites in the US and Canada switched from ATO IP to ARI and 675 subjects remained on ATO IP at or after week 52	(1533 subjects were ongoing at data cutoff of 22-SEPT-2014)			
20120104	Phase 3, multi-center, double-blind, randomized, active comparator- and placebo-controlled with induction, withdrawal, retreatment, rescue, and open-label extension phases	<p>Induction: placebo or brodalumab 140 or 210 mg SC Q2W + week 1 (day 1 to week 10) [0.5 mL and 1 mL PFS] or ustekinumab 45 or 90 mg SC (day 1 and week 4)</p> <p>Maintenance: brodalumab 140 mg SC Q2W, Q4W, or Q8W or brodalumab 210 mg SC Q2W (weeks 12 to 52 or inadequate response) or ustekinumab 45 or 90 mg SC Q12W (weeks 16 to 40 or inadequate response at week 16)</p> <p>Rescue: Brodalumab 210 mg SC Q2W or ustekinumab 45 or 90 mg SC Q12W</p> <p>OLE: Brodalumab 140 mg SC Q2W, Q4W, or Q8W or brodalumab 210 mg SC Q2W (weeks 52 to 266 or inadequate response)</p>	<p>1881/1816</p> <p>1799/906</p> <p>827/743</p> <p>1656 completed week 52 visit (1597 subjects were</p>	<p>Total: 266 weeks Primary analysis: 52 weeks</p>	<p>PASI75, sPGA BSA, PSSI, SSA, NAPS1, PROs cCSSRs, PHQ-8, safety and PK</p>	<p>Subjects with stable moderate to severe plaque psoriasis for ≥ 6 months</p> <p>Biologic therapy candidate BSA involvement ≥ 10% PASI score ≥12 sPGA ≥ 3</p> <p>Age 18 to 75 years</p>

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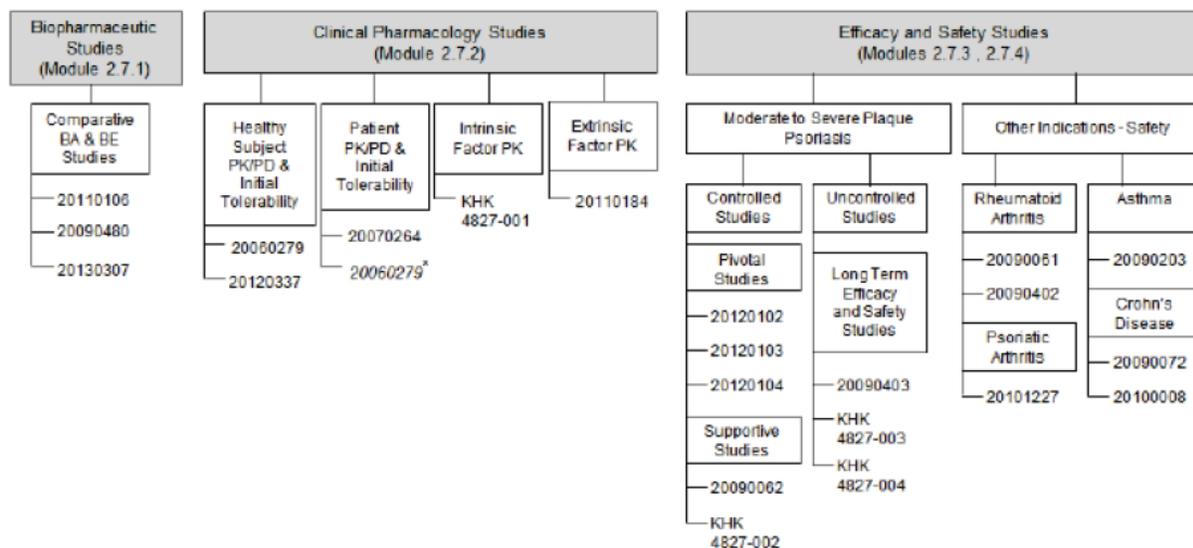
			ongoing at data cutoff of 30-AUG-2014			
20090062	Phase 2, multi-center, randomized, double-blind, placebo-controlled, multiple-dose	Brodalumab 70, 140, or 210 mg SC Q2W + week 1 (day 1 to week 10) or brodalumab 280 mg SC Q4W (day 1 and weeks 4 and 8) + placebo (weeks 1, 2, 6, and 10) or placebo Q2W + week 1 (day 1 to week 10) [70 mg/mL vial]	198/184	22 weeks	Efficacy (PASI, sPGA, BSA, PROs), safety and PK	Subjects with stable moderate to severe plaque psoriasis for ≥ 6 months BSA involvement ≥ 10% PASI score ≥ 12 Received or candidate for photo/systemic psoriasis therapy Age 18 to 70 years

Source: Adapted from Summary of Clinical studies applicant submission of BLA 761032

5.2. Review Strategy

The clinical development program for brodalumab (AMG-827) consists of eighteen studies conducted by the applicant and 4 studies conducted exclusively in Japan by partner Kiowa Hakko Kirin (KHK). The four studies conducted in Japan will not be available for review.

Figure 3: Diagram of Studies Supporting Psoriasis Indication



The focus of the efficacy and safety review will be on the three supporting Phase 3 and a single Phase 2 clinical trials in plaque psoriasis. Studies in rheumatoid arthritis, psoriatic arthritis, asthma, and Crohn’s disease will provide supporting safety evidence; [REDACTED] (b) (4)

All three pivotal clinical trials included multiple dosing regimens. Only the 210 mg dose was proposed by the applicant for marketing. Clinical trial 103 and 104 included an active control arm with ustekinumab. All studies were done across centers in Europe, Canada, Australia, and the US. Section 6 will describe the two identical trials 103 and 104. Clinical trial 102 and 062 will not be described in detail.

6 Review of Relevant Individual Trials Used to Support Efficacy

6.1. A Phase 3 Study to Evaluate the Efficacy and Safety of Induction and

Maintenance Regimens of Brodalumab Compared with Placebo and Ustekinumab in Subjects with Moderate to Severe Plaque Psoriasis: AMAGINE-2

6.1.1. Study Design

Overview and Objective

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

The trial is also designed to evaluate the efficacy of brodalumab (210 mg Q2W; and 140 mg Q2W for subjects \leq 100 kg and 210 mg Q2W for subjects $>$ 100 kg) in clearing psoriasis in subjects with moderate to severe plaque psoriasis, as measured by the proportion of subjects achieving PASI 100 at week 12.

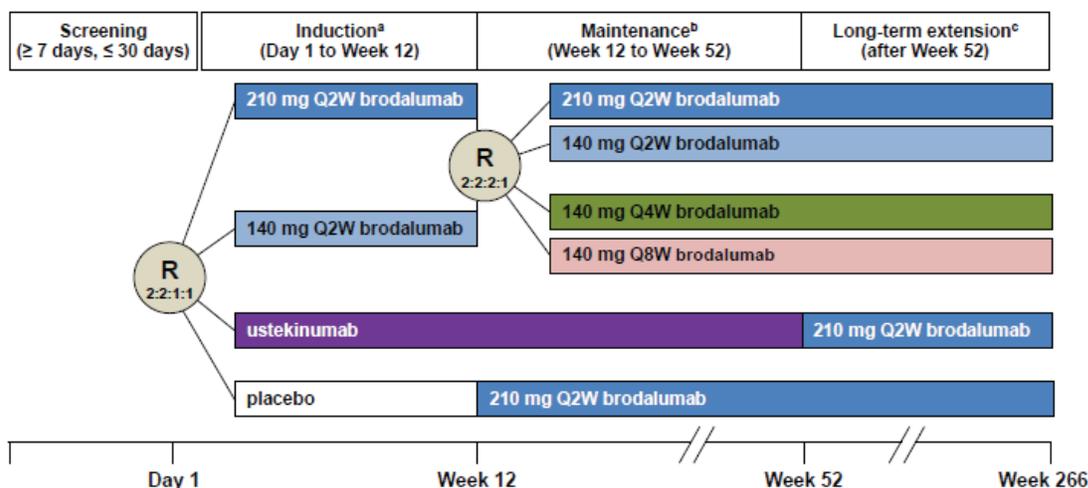
Trial Design

This study was designed to evaluate the efficacy and safety of the induction phase (12 weeks) regimens and maintenance (week 12 to week 52) phase regimens of brodalumab compared with placebo and ustekinumab in subjects with moderate to severe plaque psoriasis as measured by improvements in the Psoriasis Area and Severity Index and the static Physician's Global Assessment.

After screening, subjects entered a 12-week, randomized, double-blind, placebo- and active-controlled phase (induction phase) during which they received subcutaneous (SC) injections of brodalumab (or placebo to match brodalumab) and SC injections of ustekinumab (or placebo to match ustekinumab). Subjects were rerandomized at week 12 when they entered the maintenance phase. At week 52, subjects could continue on the study in the long-term extension phase.

Primary completion was defined as the time when the last subject was assessed or received an intervention for the purposes of final collection of data for the primary analysis (i.e., the last subject reached week 52 or terminated the study). Treatment assignments remain blinded until all subjects reached week 52 or the study terminated.

Figure 4: Study Design for 20120103 and 20120104



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.

Eligible subjects were men and women who were ≥ 18 and ≤ 75 years of age at the time of screening with stable moderate to severe plaque psoriasis diagnosed ≥ 6 months before first dose of investigational product, with involved BSA ≥ 10%, PASI ≥ 12, and sPGA ≥ 3 at screening and at baseline.

Clinical trial 20120102 is of similar design minus the active comparator ustekinumab. This trial design will not be discussed in detail.

Reviewer’s comment: Note the lack of placebo comparator after the 12-week primary endpoint. All subjects were transitioned into brodalumab. The active ustekinumab arm received maintenance doses of the active comparator until the 1 year period, and then all were switched to brodalumab.

Study Endpoints

Psoriasis Area and Severity Index (PASI): Calculation of plaque qualities (score 0 to 72), including induration, erythema, and desquamation, and the area involved with psoriasis for each body location (i.e., head and neck, upper extremities, trunk, and lower extremities). Higher scores indicate more severe and/or extensive psoriasis. PASI 50 Response is a 50% or greater improvement from baseline in PASI score, PASI 75 Response is a 75% or greater improvement, PASI 90 Response is a 90% or greater improvement, and PASI 100 Response is a 100% improvement from baseline in PASI score.

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Static Physician's Global Assessment (sPGA): The assessor's global assessment of the subject's psoriasis (defined categories: 0 [clear] to 5 [very severe]) based on severity of induration, scaling, and erythema. sPGA success is defined as a score of 0 (clear) or 1 (almost clear) and sPGA clear is defined as a score of 0. sPGA inadequate response is defined as a score of 3 (or higher), or persistent sPGA values of 2 over \geq a 4-week period at or after week 16 indicates. sPGA non-response is defined as a persistent score of \geq 3.

Statistical Analysis Plan

The first set of primary hypotheses for this study was that brodalumab at 210 mg Q2W and 140 mg Q2W would demonstrate superior efficacy compared with placebo in subjects with moderate to severe plaque psoriasis, as measured by the proportion of subjects with success based on sPGA and by the proportion of subjects with a PASI 75 at week 12.

The second set of primary hypotheses for this study was that brodalumab (at the 210 mg dosage and at the 140 mg dosage for subjects \leq 100 kg with 210 mg dosage for subjects $>$ 100 kg) would demonstrate superior ability to clear psoriasis compared with ustekinumab in subjects with moderate to severe plaque psoriasis, as measured by the proportion of subjects attaining PASI 100 at week 12.

It was further hypothesized that subjects with moderate to severe plaque psoriasis who continued to receive brodalumab 210 mg Q2W or 140 mg Q2W would demonstrate superior response compared to those randomized to receive brodalumab at lower frequencies in the maintenance phase (140 mg Q4W and 140 mg Q8W), as measured by the proportion of subjects with success based on sPGA at week 52.

For comparisons in the placebo family and ustekinumab family at week 12, the significance level, alpha, was 0.01 and 0.04, respectively. After rerandomization at week 12, the maintenance phase endpoint (sPGA success at week 52) was tested at full alpha = 0.05.

Data Quality and Integrity: Sponsor's Assurance

Administration of this study by Amgen was the responsibility of the brodalumab clinical study team, which included representatives from appropriate departments, including Biostatistics, Clinical Development, Global Regulatory Affairs, Health Economics, Medical Sciences, and Safety. Specifically, the clinical study team designed the protocol and electronic case report forms (eCRFs), monitored the study, entered the data into the clinical database, analyzed the data; assure that the study and data is accurate to the best of their knowledge.

6.1.2. Study Results

Compliance with Good Clinical Practices

CDER Clinical Review Template 2015 Edition
Version date: November 5, 2015 for initial rollout (NME/original BLA reviews)

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The clinical study program was carried out in accordance with Good Clinical Practice (GCP), as documented by the ICH and the US FDA.

Financial Disclosure

In compliance with 21 CFR Part 54, Amgen forwarded a Certification/Disclosure Form to the clinical investigators and sub-investigators who participated in covered clinical studies for brodalumab, as described in the protocols. Prior to study initiation, the investigators were requested to certify to the absence of certain financial interests or arrangements or to disclose, as required, those financial interests or arrangements as delineated in 21 CFR 54.4(a)(3)(i-iv). In addition, investigators were requested to notify Amgen if there is any change to the information given for up to one year after the study ended. No clinical investigators and/or sub-investigators who participated in the studies are full or part-time employees of Amgen.

Patient Disposition

The following discussion will be on the pooled safety population with focus on the pivotal and supportive controlled studies making up the bulk of the safety and efficacy data.

Figure 5: Summary of Efficacy and Safety Studies

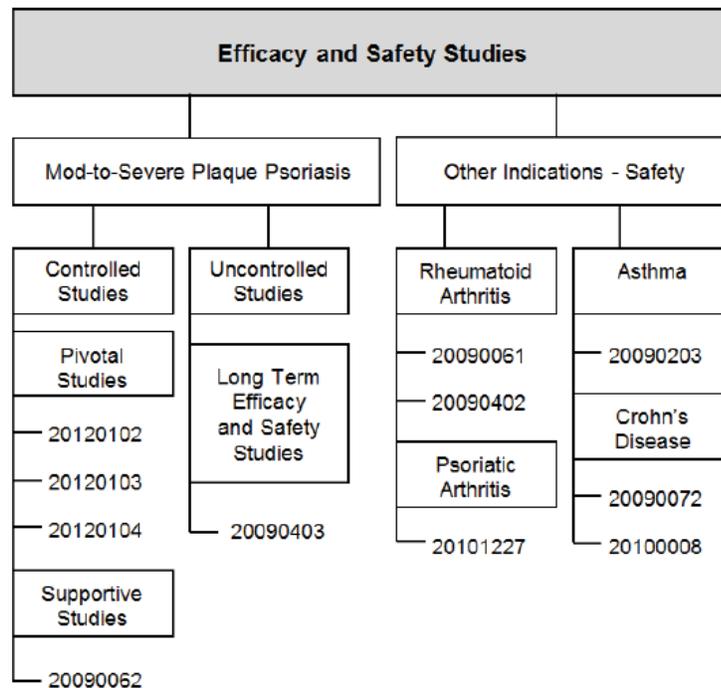
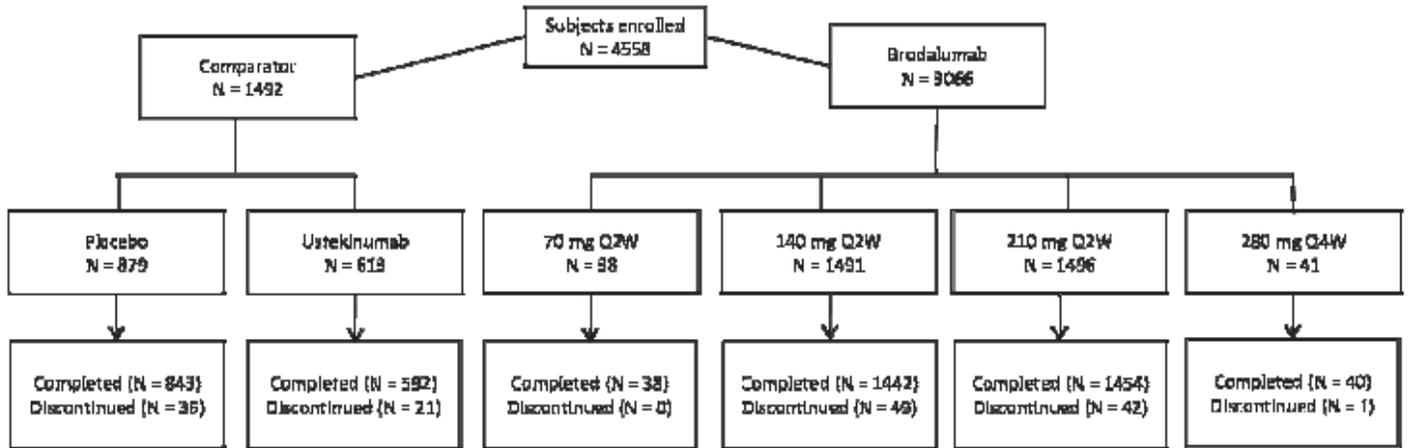
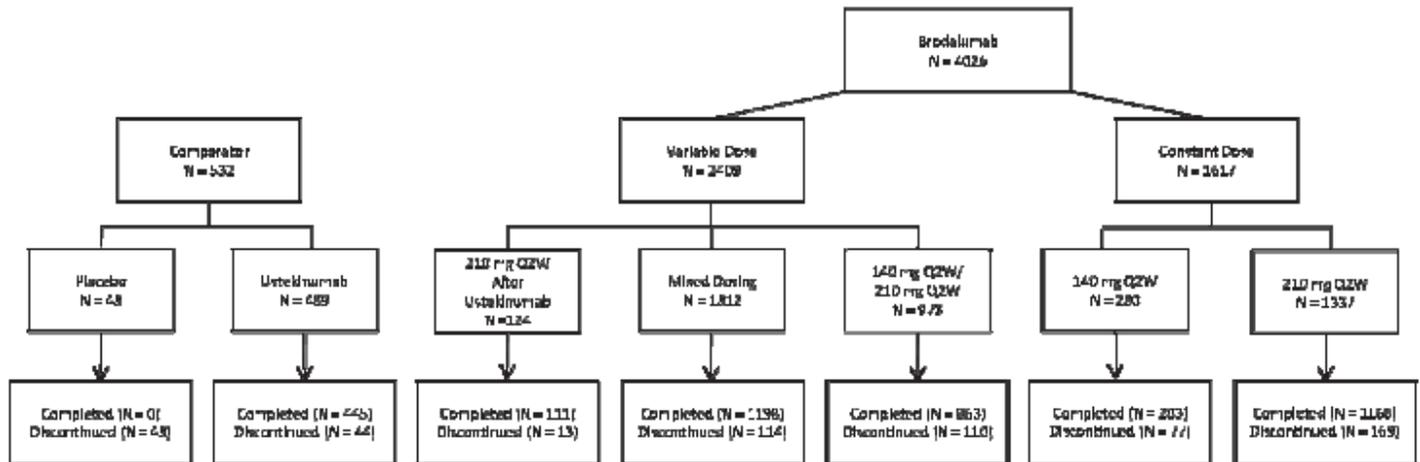


Figure 6: Subject disposition for Induction (12-week Controlled)



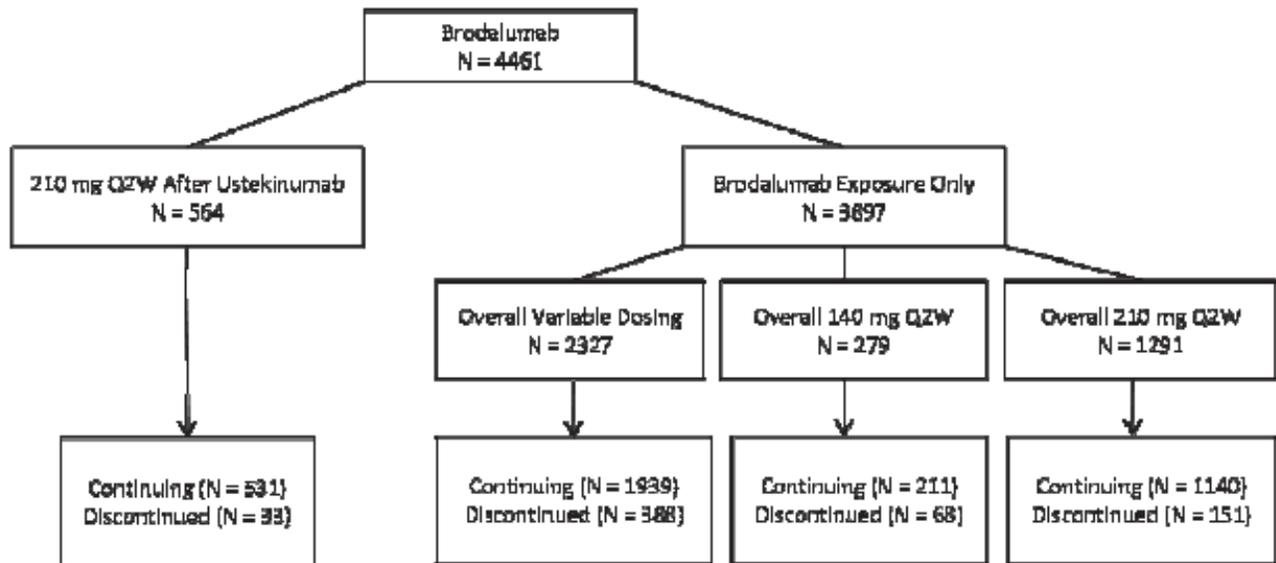
Source: ISS Table 14-1.1.1

Figure 7: Subject disposition for long-term maintenance (first 52 weeks)



Source: ISS Table 14-1.1.5

Figure 8: Subject disposition through data cut off



Source: ISS Table 14-1.1.8

Reviewer’s comments: Several things to note about the design of the clinical trials 102/103/104 in regard to disposition of subjects; 1. Placebo subjects completing the induction phase (12-weeks) are switched to brodalumab. 2. Ustekinumab subjects in the open-label long-term extension phase (52-weeks) all switched to brodalumab. 3. Few subjects completed the entire trial on placebo or ustekinumab, generally due to discontinuations. The majority of subjects were in the 210 mg Q2W arm.

Table of Demographic Characteristics

Baseline demographics and baseline physical characteristics were generally similar across treatment and dose groups. Disease characteristics were also equal among treatment arms. The majority of the subjects were male, in their 45-64 years of life, and 15% had some depression at baseline.

Reviewer’s comment: The fact that a majority of subjects were male, between the ages of 45-64, with 15% previous depression was an important point in consideration of the suicide signal discovered in these clinical trials.

Table 4: Baseline demographics and characteristics – Safety Analysis

n (%)	Brodalumab n = 3066	Placebo n = 879	Ustekinumab n = 613
Sex			
Male	2124 (69)	607 (69)	417 (68)
Age			
Mean years (SD)	44.8 (13)	44.6 (13)	45.1 (13)
< 40 years	1111 (36)	347 (39)	220 (36)
45-64 years	1763 (58)	476 (54)	351 (57)
≥ 65 years	192 (6)	56 (6)	42 (7)
Race			
White	2775 (90.9)	799 (90.9)	551 (89.9)
Black or African American	85 (2.8)	29 (3.3)	20 (3.3)
Asian	116 (3.8)	29 (3.3)	24 (3.9)
American Indian or Alaska Native	16 (0.5)	2 (0.2)	1 (2.6)
Native Hawaiian or Other Pacific Islander	18 (0.6)	3 (0.3)	1 (0.2)
Other ¹	52 (1.7)	15 (1.7)	15 (2.4)
Psoriatic Arthritis			
YES	654 (21.3)	180 (20.5)	114 (18.6)
Psoriasis Duration (years)			
N	3065	879	613
Mean	18.4	18.5	18.5
SD	12.1	12.0	12.2
Previous biologic Usage	874 (29)	266 (30)	160 (26)
Psychiatric Disorders	538 (18)	150 (17)	121 (20)
Depression	430 (14)	117 (13)	98 (16)

Source: Reviewer adapted table, ISS

Other Baseline Characteristics (e.g., disease characteristics, important concomitant drugs)

The reported medical and/or surgical history of subjects in the psoriasis studies was consistent with the disease population and known comorbidities and was generally well balanced across treatment groups. Overall, >80% of subjects reported ≥ 1 medical or surgical history condition. Individual CV risk factors in the all-brodalumab group included hypertension (26.6%), obesity (8.0%), hypercholesterolemia (7.0%), hyperlipidemia (6.3%) and type 2 diabetes mellitus (6.1%). Psychiatric comorbidities were reported for 17.5% of brodalumab treated subjects and included depression (10.0%), anxiety (5.5%), suicidal ideation (0.8%), and suicide attempt (0.3%). Psychiatric history was based on self-report and will be discussed in the analysis section.

7 Integrated Review of Effectiveness

7.1. Assessment of Efficacy across Trials

7.1.1. Primary Endpoints

The applicant submitted results from three randomized, double-blind, multicenter, placebo-controlled Phase 3 trials (Studies 20120102, 20120103, 20120104) with Trials 03 and 04 that also included an active, ustekinumab arm.

All trials enrolled subjects 18 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.

Table 5: Summary of Primary and Secondary Endpoints in Trials 02, 03, and 04

	Comparison against placebo		Comparison against ustekinumab	
		Trials 02, 03, 04	Endpoint	Trials 03 and 04 ⁽²⁾
Primary	PASI 75	210 mg vs. placebo	PASI 100	210 mg vs. ustekinumab
	sPGA 0 or 1			
	PASI 75	140 mg vs. placebo		Weight-based ⁽¹⁾ vs. ustekinumab
	sPGA 0 or 1			
Key secondary	PASI 100	210 mg vs. placebo	PASI 100	140 mg vs. ustekinumab
	sPGA of 0	140 mg vs. placebo	PASI 75	Weight-based ⁽¹⁾ vs. ustekinumab
	PASI 100			
	sPGA of 0			
	PSI ⁽³⁾	210 mg vs. placebo		
responder	140 mg vs. placebo			

Source: reviewer table

- (1) Weight-based: Brodalumab 140 mg for subjects ≤100 kg; brodalumab 210 mg for subjects >100 kg;
- (2) For Trials 03 and 04, the allocation of α for the comparison with ustekinumab was 0.04, and for the comparison with placebo, α=0.01.
- (3) Psoriasis Symptom Inventory. PSI responder was defined as total score ≤ 8, with no item score > 1 at Week 12.

According to the applicant, ustekinumab was chosen as the active control in Trials 03 and 04 because it was the most efficacious available treatment at the time of study design and was predicted to be the most commonly used treatment option at the time of approval. The applicant stated that ustekinumab was sourced from the U.S. and dosed according to the dosing recommendations provided in the US and European Union labeling. With the ustekinumab arm in Trials 03 and 04, the applicant conducted an additional family of hypothesis testing (i.e., brodalumab vs. ustekinumab) in addition to the hypothesis testing of brodalumab vs. placebo, and prespecified a significance level of 0.01 and 0.04 for the comparisons against placebo, and against ustekinumab, respectively.

For all trials, both brodalumab doses were superior to placebo (p<0.001) for the co-primary (PASI 75 and sPGA of 0 or 1 at Week 12) as well as the secondary endpoints (PASI 100, sPGA of 0, and Psoriasis Symptom Inventory (PSI) responder at Week 12). For the comparison of brodalumab against ustekinumab, brodalumab 210 mg as well as the weight-based brodalumab (210 mg for subjects >100 kg, and 140 mg for subjects ≤100 kg) dose were superior to ustekinumab (p<0.001) for the primary endpoint of PASI 100 at Week 12; however, the efficacy analysis for comparing brodalumab 140 mg against ustekinumab was not statistically significant (p=0.078) for PASI 100 at Week 12 in Trial 03.

Table 6: Results of the Co-Primary and Key Secondary Efficacy Endpoints at Week 12 for Clinical Trials 02, 03, 04 (ITT, NRI)

		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 (0.6%)	65 (22%)	205 (34%)
	sPGA of 0	274 (45%)	157 (26%)	2 (0.6%)	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;

- (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.

Cochran-Mantel Haenszel (CMH) test stratified by baseline body weight (≤100 kg vs. >100kg), prior biologic use (yes, no), geographic region, and baseline value of the endpoint (≤ median, >median for PASI, 3, 4, 5 for sPGA). Missing data was imputed using non-responder imputation (NRI).

Reviewer's comment: *The efficacy of brodalumab is consistent with the two IL-17A ligand antagonists on the market (ixekizumab and secukinumab). The PASI 75 response ranges approximate 84% and the sPGA of 0 is 40%. Weight based therapy does not seem to change the efficacy results, although there does seem to be some benefit to be able to give the 140 mg dose to lighter subjects, as the efficacy response does not change. There does not seem to be a benefit in terms of safety with the reduced dosing for lighter subjects. This reviewer is in agreement with the standard 210 mg dosing schedule proposed by the applicant.*

7.1.2. Secondary and Other Endpoints

For all three pivotal trials, 02, 03 and 04; 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.

The Psoriasis Symptom Inventory (PSI) consisted of 8 psoriasis-specific items (itch, redness, scaling, burning, stinging, cracking, flaking, and pain) which was collected using an electronic Diary (eDiary). Subjects rated the severity of each of the 8 items from “not at all” to “very severe” ranging from 0 to 4 with total scores from 0 to 32 with higher scores indicating worse symptoms.

For the comparison of brodalumab vs. ustekinumab, the protocol-specified secondary endpoints were:

- The proportion of subjects with PASI 100 at Week 12 for the comparison of brodalumab 140 mg Q2W vs. ustekinumab.
- The proportion of subjects with PASI 75 at Week 12 for the comparison of weight-based brodalumab dose vs. ustekinumab.

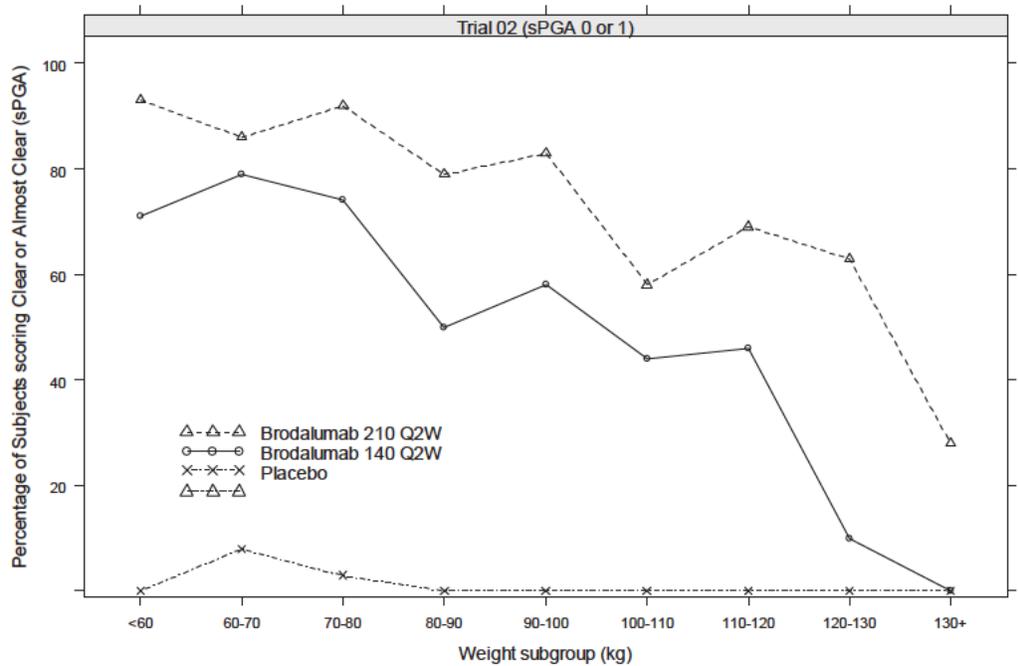
The sets of comparisons (i.e., against placebo or against ustekinumab) and the corresponding primary and secondary endpoints are summarized in **Table 5**.

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 of 0 or 1, as well as the key secondary endpoint of PASI 100, sPGA of 0, and PSI responder at Week 12 for both brodalumab doses compared to placebo in all three trials. For Trials 03 and 04, brodalumab 210 mg and the weight-based brodalumab dose were superior to ustekinumab on the primary endpoint of PASI 100 ($p < 0.001$ and $p = 0.0007$, respectively); however, for the comparison of brodalumab 140 mg vs. ustekinumab, only Trial 04 was statistically significant ($p\text{-value} = 0.007$), and Trial 03 was not ($p\text{-value} = 0.078$).

7.1.3. Subpopulations

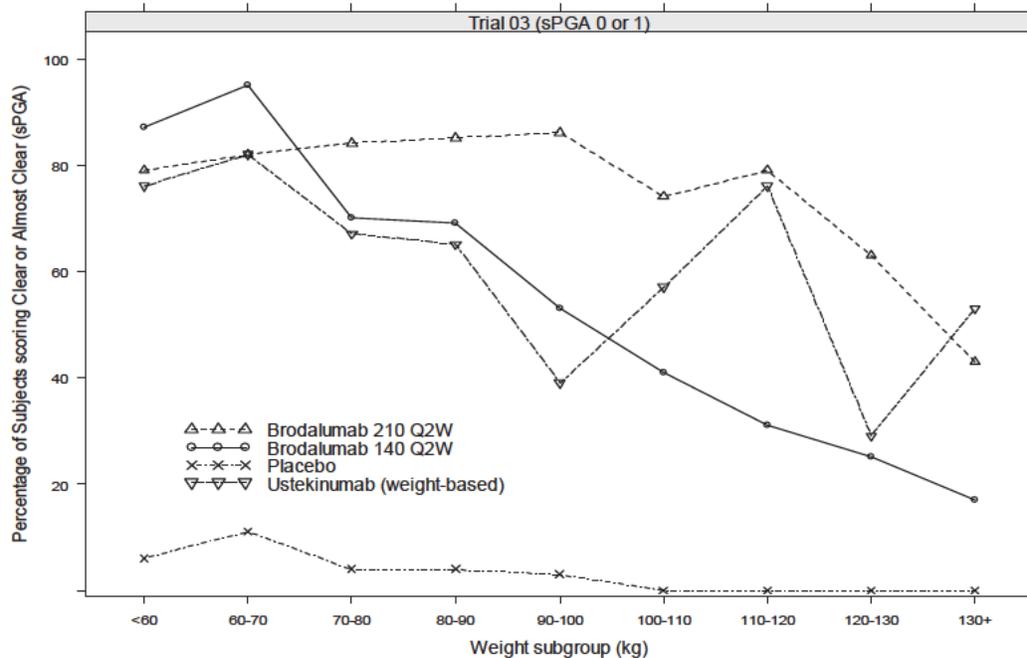
One of the randomization stratification factors was to stratify by baseline body weight (≤ 100 kg vs. > 100 kg), and because ustekinumab is approved for weight-based dosing (45 mg for subjects ≤ 100 kg and 90 mg for subjects > 100 kg), the biostatistics reviewer evaluated the sPGA response (0 or 1) rates for the two brodalumab doses at Week 12 by weight in 10 kg increments. In all three pivotal trials (Trials 02, 03, 04), brodalumab 210 mg Q2W generally had higher sPGA response rates than the responses of the 140 mg Q2W dose group across most weight subgroups. Trials 03 and 04 included an ustekinumab arm, and its sPGA response at Week 12 by weight is shown for those trials as well. **Figures below** present the sPGA success at Week 12 by weight in 10 kg increments for Trials 02, 03, and 04, respectively.

Figure 9: Success on the sPGA(1) at Week 12 by Weight (in 10 kg increments) for Trial 02



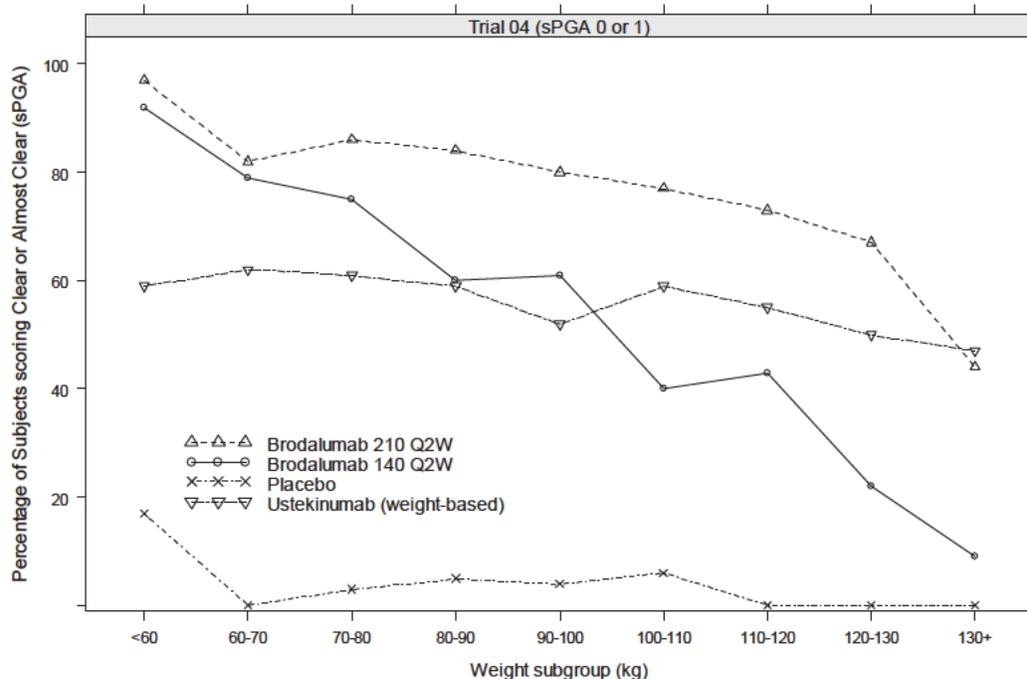
Source: Reviewer's figure. (1) sPGA of 0 or 1

Figure 10: Success on the sPGA(1) at Week 12 by Weight (in 10 kg increments) for Trial 03



Source: Reviewer's figure. (1) sPGA score of 0 or 1.

Figure 11: Success on the sPGA(1) at Week 12 by Weight (in 10 kg increments) for Trial 04



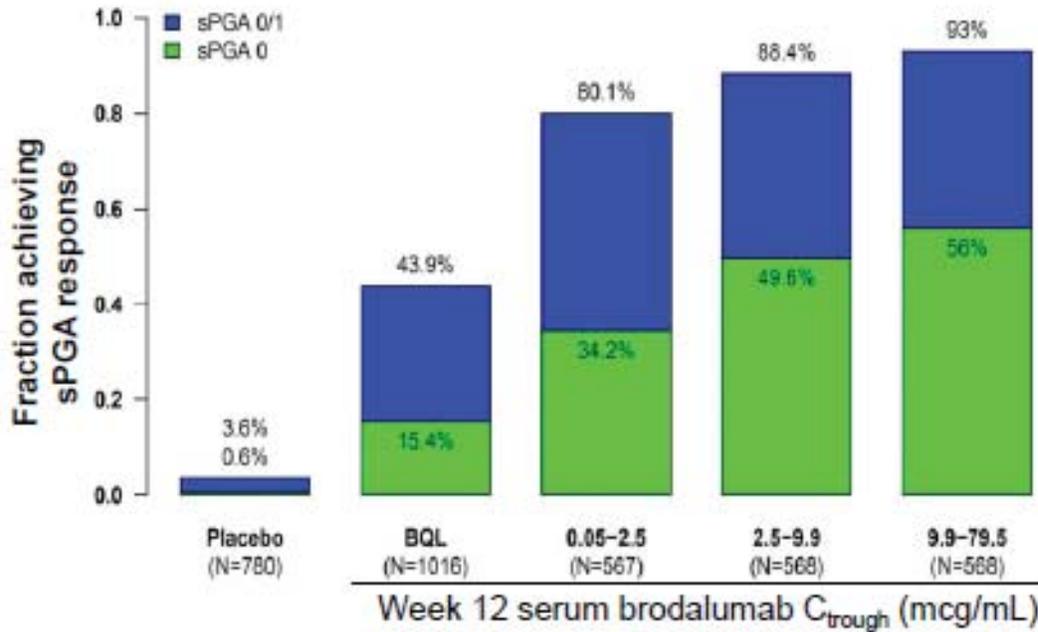
Source: Reviewer's figure. (1) sPGA score of 0 or 1.

Reviewer's comment: The brodalumab 210 mg dosing was more effective than the 140 mg dosing regimen. The brodalumab product exhibits a non-linear PK and weight affects the concentration (clearance increases as BW decreases).

7.1.4. Dose and Dose-Response

The dose-exposure response for brodalumab is outlined in the Clinical Pharmacology review. A brief summary will be provided.

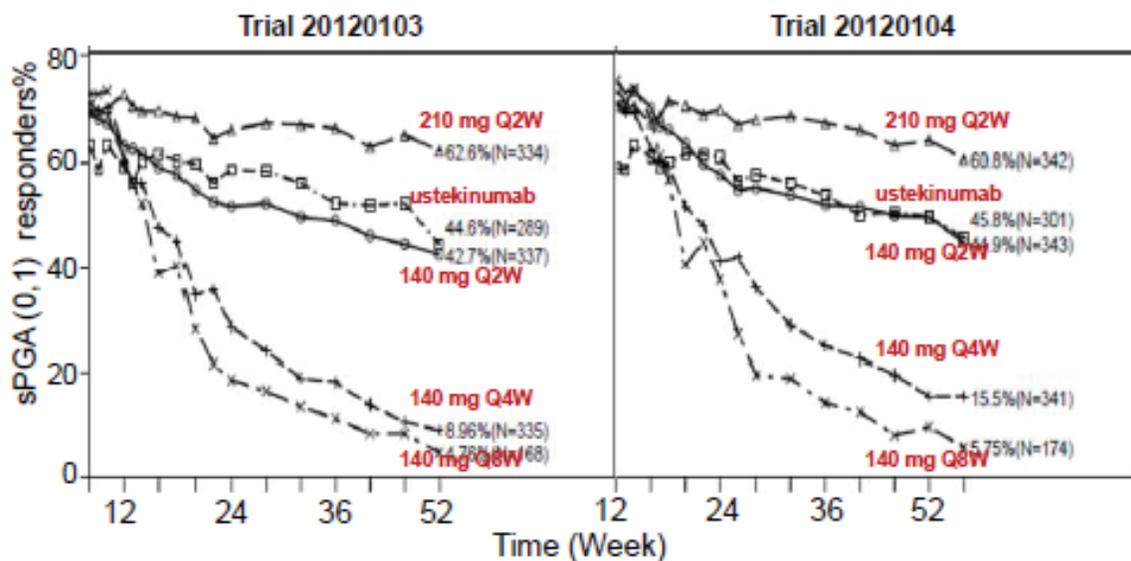
Figure 12: Week 12 Efficacy: Exposure-Response



Source: Summary of Clinical Pharmacology Review

The pharmacokinetic data suggest that the higher the serum concentration of brodalumab, the better the efficacy.

Figure 13: Week 52 Efficacy Results: sPGA (0,1)



Source: Clinical Pharmacology Review

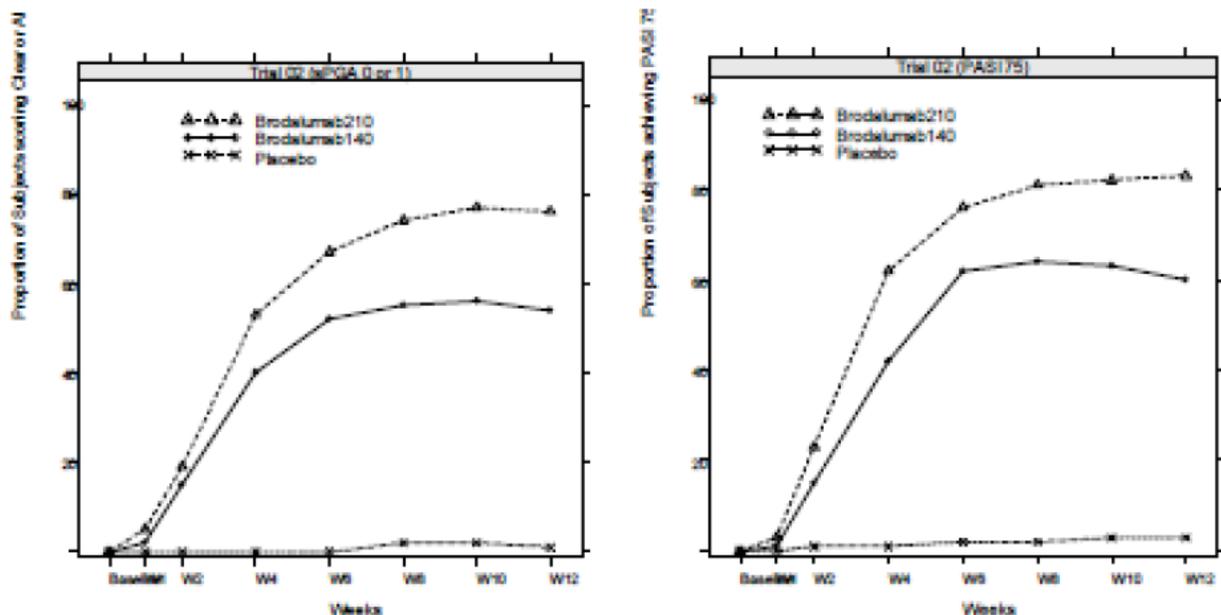
The 210mg Q2W appears to have the most efficacious result in response to maintenance out to 52 weeks.

Reviewer's comment: The applicant has appropriately evaluated the dose-response relationship with brodalumab in the treatment of moderate to severe plaque psoriasis. This review is in agreement with the selected dose of 210 mg at 0, 1, and 2 week then Q2W for the efficacy of this product.

7.1.5. Onset, Duration, and Durability of Efficacy Effects

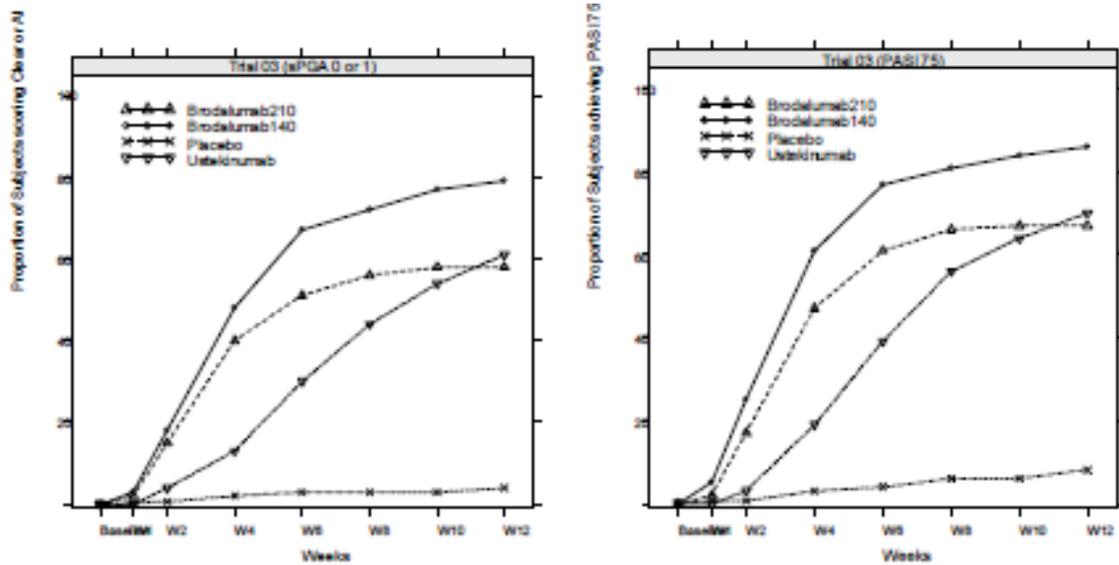
For the induction period, subjects were evaluated for sPGA and PASI scores on Weeks 1, 2, 4, 6, 8, 10, and 12. The following graphs Figures 10, 11, and 12 show the results of the proportion of subjects with sPGA of 0 or 1 as well as the proportion of subjects achieving PASI 75 during the induction period for Trials 02, 03, and 04, respectively.

Figure 14: Success on the sPGA⁽¹⁾ and PASI 75 response for the Induction Period of Trial 02



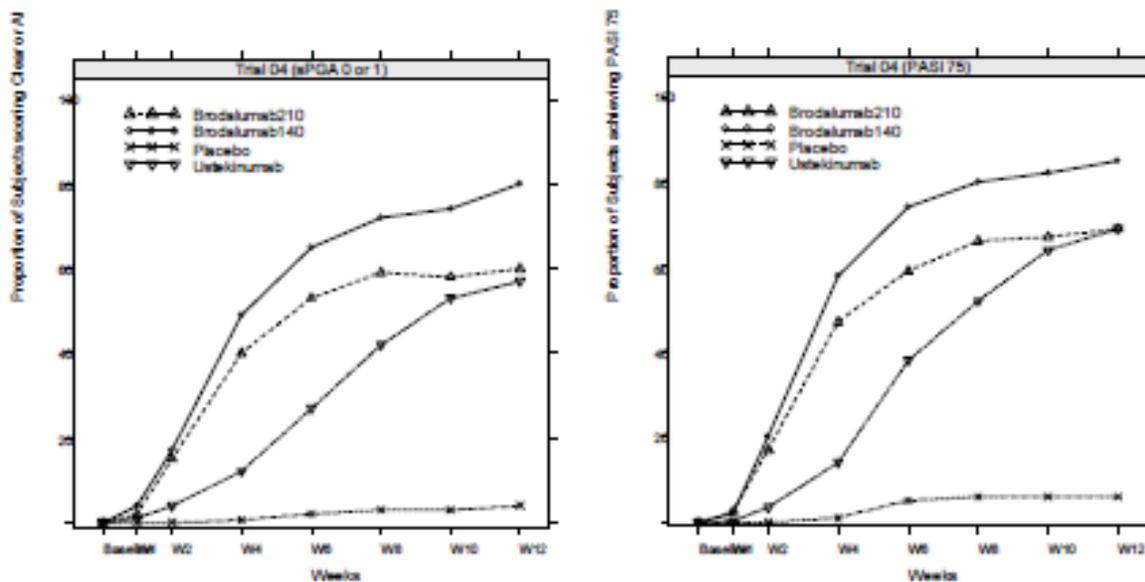
Source: reviewer figures; Intent-to-Treat (ITT) analysis set; Missing data was imputed using non-responder imputation (NRI).
 (1) sPGA score of 0 or 1.

Figure 15: Success on the sPGA⁽¹⁾ and PASI 75 response for the Induction Period of Trial 03



Source: reviewer figures; Intent-to-Treat (ITT) analysis set; Missing data was imputed using non-responder imputation (NRI).
 (1) sPGA score of 0 or 1.

Figure 16: Success on the sPGA⁽¹⁾ and PASI 75 response for the Induction Period of Trial 04



Source: reviewer figures; Intent-to-Treat (ITT) analysis set; Missing data was imputed using non-responder imputation (NRI).
 (1) sPGA score of 0 or 1.

Trials 03 and 04 evaluated maintenance of sPGA success at Week 52 and conducted pairwise sequential hypothesis test; however, 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. Further, the Agency stated that the pairwise sequential hypothesis test comparisons between selected maintenance regimens may have limited utility for identifying the appropriate regimen. Subjects with sPGA of 0 or 1 response at Week 52 was higher among those subjects that received the brodalumab 210 mg Q2W than those that received the lower doses of brodalumab (i.e., 140 mg Q2W; 140 mg Q4W; 140 mg Q8W). **Table 7** presents the proportion of Week 12 sPGA responders (i.e., scoring sPGA of 0 or 1) who maintained sPGA responders at Week 52. Among those subjects that were sPGA responders at Week 12, the proportion of subjects that maintained their responder status was highest in those that received brodalumab 210 mg dose (79%).

Table 7: Maintenance of sPGA Response⁽¹⁾ at Week 52 for Trials 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%)	135/234 (58%)	28/240 (12%)	7/123 (6%)
04	sPGA 0 or 1	190/242 (79%)	143/254 (56%)	48/244 (20%)	9/132 (7%)

Source: Applicant's analysis. (1) sPGA of 0 or 1. The applicant defined non-responder as having a single sPGA =3 or persistent sPGA of at least for at least 4 weeks on or after Week 16. This reviewer considered non-responder for those that do not meet the success criteria of sPGA of 0 or 1 at Week 52.

Trial 02 included a randomized withdrawal period following the 12-week induction period, and sPGA responders (sPGA of 0 or 1) at Week 12 were randomized in a 1:1 to either continue the brodalumab dose that they received in the induction period or placebo. Subjects that continued to receive brodalumab dose had higher sPGA 0 or 1 response rates at Week 52 compared to those that were re-randomized to placebo. The sPGA of 0 or 1 response at Week 52 among those subjects that were sPGA responders at Week 12 are summarized in **Table 8** below.

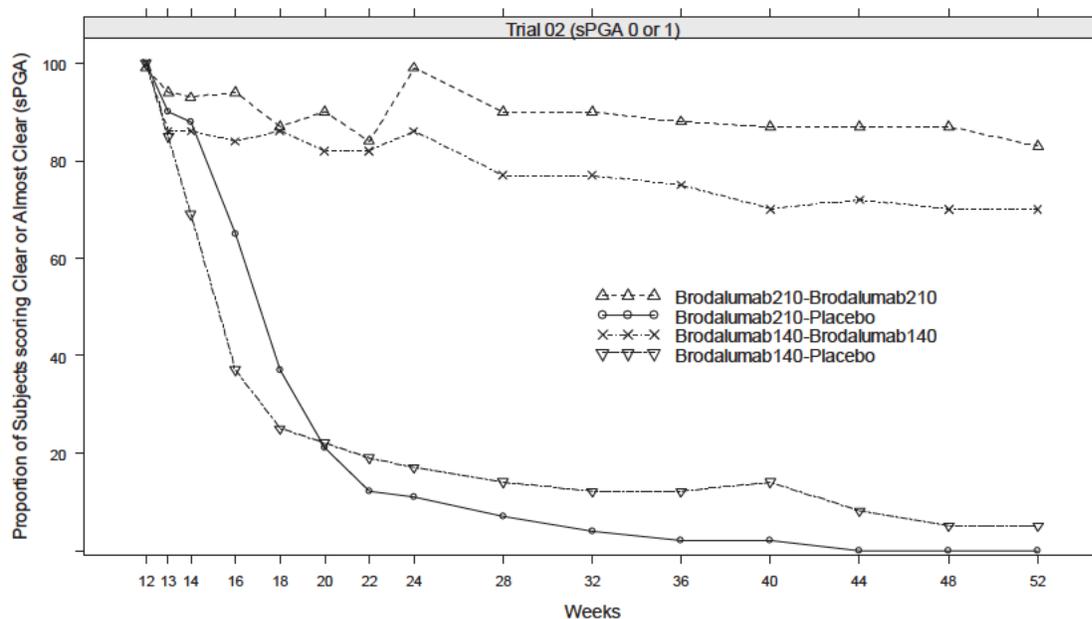
Table 8: Success on the sPGA⁽¹⁾ at Week 52 for Trials 02 during the Randomized Withdrawal

Induction Dose		Brodalumab 210 mg Q2W		Brodalumab 140 mg Q2W	
Randomized Withdrawal		Brodalumab 210 mg Q2W	Placebo	Brodalumab 140 mg Q4W	Placebo
Trial 02	sPGA 0 or 1	69/83 (83%)	0/84 (0%)	40/57 (70%)	3/59 (5%)

Source: Reviewer's analysis. (1) sPGA of 0 or 1.

Figure 17 presents the response rates (sPGA 0 or 1) during the randomized withdrawal for Trial 02, and Figures 18 and 19 present the sPGA 0 or 1 response rates during the maintenance period for Trials 03 and 04. For Trial 02, the proportion of subjects that maintain their response at Week 52 was higher for subjects that continued their dose received at the induction period, and those that were re-randomized to placebo lost their sPGA response during the randomized withdrawal period.

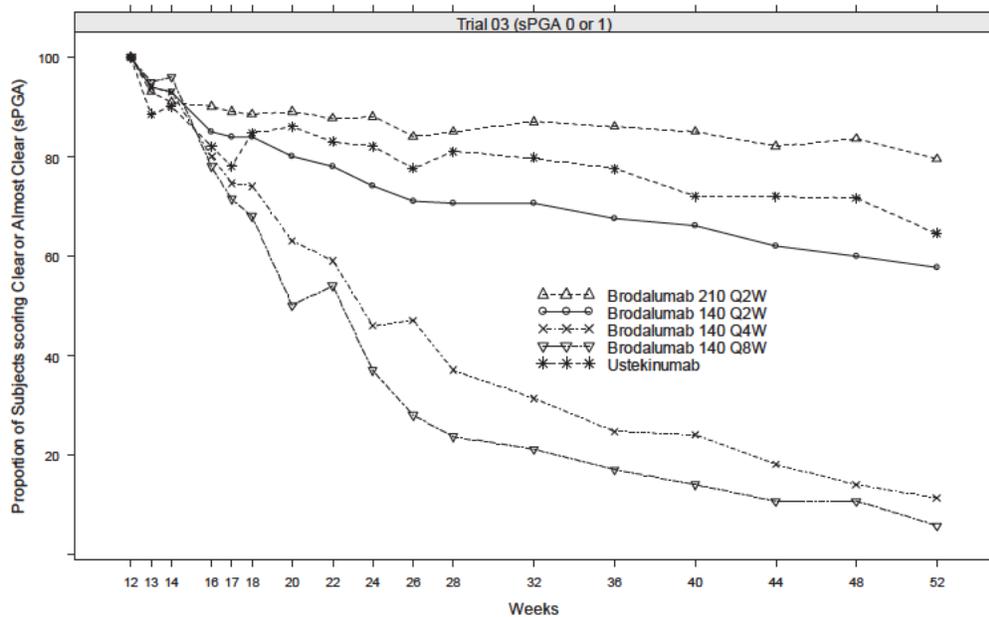
Figure 17: Maintenance of sPGA of 0 or 1 response during the Randomized Withdrawal Period (Weeks 12-52) for Trial 02



Source: Reviewer's figure

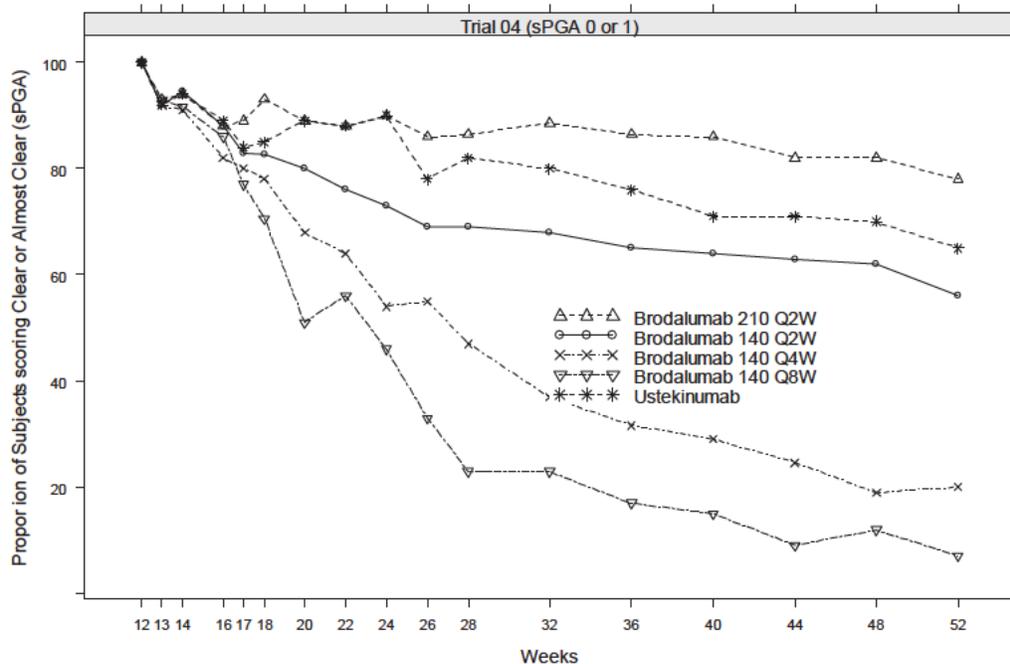
For Trials 03 and 04, the proportion of subjects that maintained their sPGA response was higher for subjects who received brodalumab 210 mg Q2W compared to brodalumab 140 mg doses (i.e, Q2W, Q4W, Q8W), and placebo. The proportion of sPGA responders that maintained their sPGA response status and received ustekinumab was higher than those subjects that received brodalumab 140 mg Q2W, but lower than those subjects that received brodalumab 210 mg Q2W as seen in Figures 18 and 19 below.

Figure 18: Maintenance of sPGA of 0 or 1 response during the Maintenance Period (Weeks 12-52) for Trial 03



Source: Reviewer's figure

Figure 19: Maintenance of sPGA of 0 or 1 response during the Maintenance Period (Weeks 12-52) for Trial 04



Source: Reviewer's figure

7.2. Additional Efficacy Considerations

7.2.1. Considerations on Benefit in the Postmarket Setting

None

7.2.2. Other Relevant Benefits

The development program for rheumatoid arthritis was discontinued due to lack of efficacy. The development program in Crohn's disease was also discontinued due to the drug causing exacerbation of Crohn's disease.

7.3. Integrated Assessment of Effectiveness

Systemic biologic therapy for moderate to severe chronic plaque psoriasis is a mainstay of treatment. Enbrel®, one of the first biologics approved for treatment of plaque psoriasis, was approved in 2004. Since 2004, multiple biologic products targeting α TNF and other cytokines in the inflammatory cascade have expanded the treatment options for the clinical management of psoriasis.

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SILIQ® (Brodalumab)

The table and figure below present descriptive comparisons of PASI 75, PGA, and PASI 100 response rates for the biologic products available on the U.S. market for treatment of moderate to severe adult psoriasis. Note that ixekizumab and secukinumab are IL17A antibodies directed at IL-17 cytokines. The mechanism of action for brodalumab is distinct in that it binds to certain IL-17 receptors rather than cytokines.

Reviewer Comment: *The effectiveness for brodalumab is similar in class for the IL-17A ligand binding products recently approved by the Agency for the treatment of plaque psoriasis (ixekizumab and secukinumab), see **table 9**. The applicant included an active comparator in the clinical trials 03 and 04 for the endpoint of PASI 100 (completely clear skin). Although this is not required for approval of the product, the comparative advantage is clear against ustekinumab. The applicant also pre-specified the endpoint for PASI 100 in the clinical trials. The only other pre-specified PASI 100 endpoint in the clinical trials is for ixekizumab. The comparison can be seen in **Figure 20**. No other biologic product has a direct head-to-head comparison in a clinical trial setting.*

The rationale for cross study comparison of efficacy is to show that other biologic products have similar efficacy of response to that of this new product. Physicians and patients have choices for recalcitrant disease when a single agent has failed.

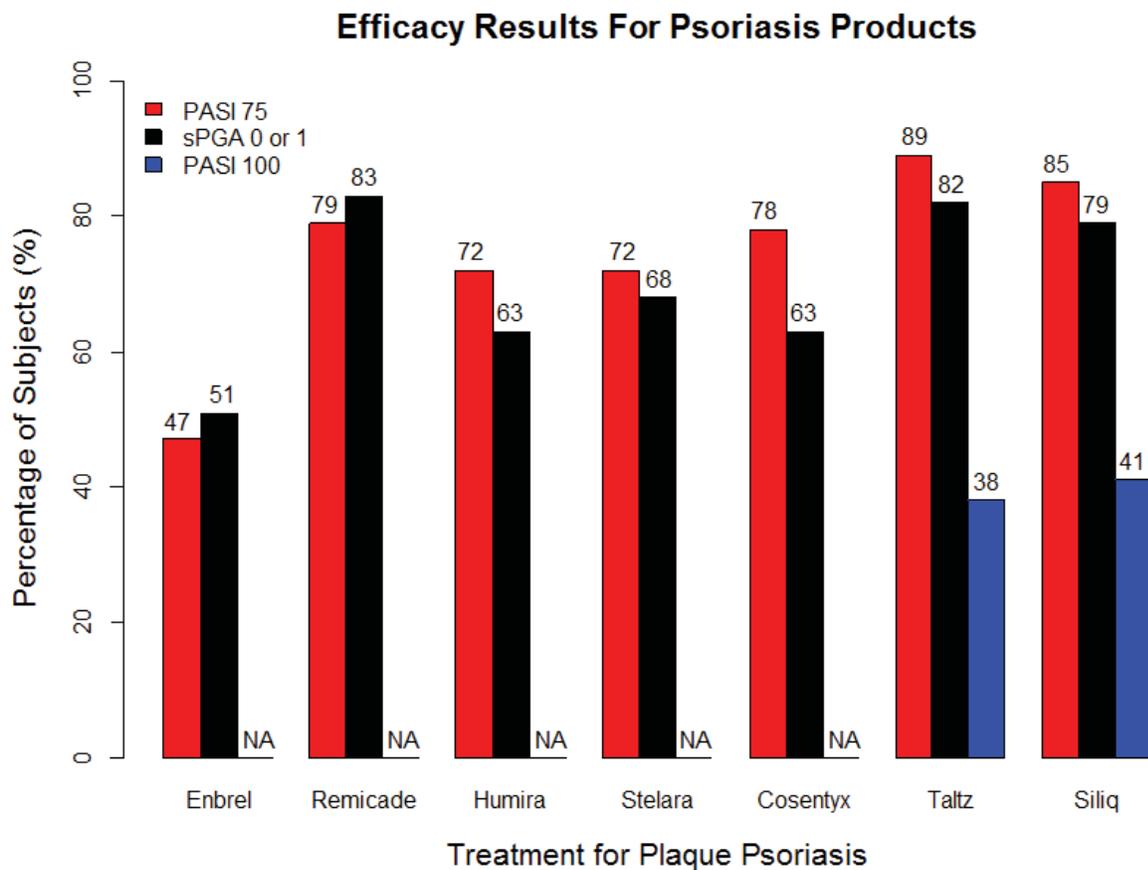
Table 9: Comparative Response Rates for Psoriasis Biologics

	Etanercept (Enbrel®)	Infliximab (Remicade®)	Adalimumab (Humira®)	Ustekinumab (Stelara®)	Ixekizumab (Taltz®)	Secukinumab (Cosentyx®) ^a	Brodalumab (Siliq®)
PASI 75	47%	79%	72%	72%	89%	78%	85%
PGA 0/1	51%	83%	63%	68%	82%	63%	79%
PASI 100	NA	NA	NA	NA	37%	NA	41%

Source: Clinical Review of Data from PI.

^a Secukinumab only included PASI 90 (56%)

Figure 20: Bar Graph of Efficacy Results for Psoriasis Biologic Products



Source: Reviewer's figure. The primary efficacy analysis timepoint for Remicade and Humira was Week 10 and 16, respectively; for others, the primary timepoint was Week 12. The descriptors for the Physician Global Assessment (PGA) scale varied across the products.

8 Review of Safety

The review of clinical safety provides an overview of short and long term safety profiles associated with brodalumab treatment in adult subjects with moderate to severe plaque psoriasis, and other indication studied. The safety population is based on the data from the three Phase 3 placebo-controlled trials (20120102, 20120103, and 20120104), of which two trials were also ustekinumab-controlled (20120103 and 20120104).

The safety population includes 5205 subjects who received ≥ 1 dose of brodalumab in Phase 2 and 3 of the clinical trials submitted by the applicant. The focus is on the data from the psoriasis trials, which 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.

8.1. Safety Review Approach

The safety review for brodalumab will focus mainly on SIB (suicide behavior, suicide attempt, suicide complete) and on Major Adverse Cardiovascular Events (MACE). The Phase 2 and three Phase 3 clinical trials revealed these two specific adverse events as safety signals of focus. General safety issues will also be touched on, but they do not appear to change the safety profile of this biologic product.

8.2. Review of the Safety Database

8.2.1. Overall Exposure

The defined exposure time included the time periods when subjects were exposed to investigational product including dosing interval and excluding any gaps/interruptions in exposure, and follow-up observation time included any gaps/interruptions exposure and including follow-up time beyond the exposure period.

Through the 120-day safety update end of study, a total of 4464 subjects with psoriasis received ≥ 1 dose of brodalumab had a total of 8655.0 patient-years of exposure and the mean duration of exposure was nearly 2 years: 1304 subjects received overall brodalumab 210 mg Q2W, 256 subjects received overall brodalumab 140 mg Q2W, 2337 subjects received variably dosed brodalumab (without ustekinumab exposure), and 567 subjects received brodalumab 210 mg Q2W after ustekinumab exposure.

Table 10: Numbers of Subjects Receiving brodalumab and Duration of Cumulative Exposure through end of study – Psoriasis Subset

	Brodalumab				
	210 mg Q2W After Ustekinumab (N=567)	Subjects who had brodalumab exposure Only			
		Overall Variable Dosing (N=2337)	Overall 140 mg Q2W (N=256)	Overall 210 mg Q2W (N=1304)	Overall All (N=4464)
Total subj-yrs exposed	715.2	4948.8	448.4	2542.6	8655.0
Total subj-yrs of follow-up	778.1	5236.4	473.6	2685.8	9173.9
Duration of cumulative exposure, n (%)					
≥1 dose	567 (100.0)	2337 (100.0)	256 (100.0)	1304 (100.0)	4464 (100.0)
≥3 months	550 (97.0)	2289 (97.9)	205 (80.1)	1251 (95.9)	4295 (96.2)
≥9 months	509 (89.8)	2099 (89.8)	188 (73.4)	1184 (90.8)	3980 (89.2)
≥12 months	396 (69.8)	2018 (86.4)	186 (72.7)	1155 (88.6)	3755 (84.1)
≥18 months	184 (32.5)	1884 (80.6)	184 (71.9)	1112 (85.3)	3364 (75.4)
≥24 months	42 (7.4)	1441 (61.7)	156 (60.9)	769 (59.0)	2408 (53.9)
≥36 months	0 (0.0)	139 (5.9)	0 (0.0)	4 (0.3)	143 (3.2)
≥48 months	0 (0.0)	130 (5.6)	0 (0.0)	3 (0.2)	133 (3.0)
≥60 months	0 (0.0)	107 (4.6)	0 (0.0)	3 (0.2)	110 (2.5)
Duration of cumulative exposure (months)					
n	567	2337	256	1304	4464
Mean	15.14	25.41	21.02	23.40	23.27
SD	5.83	12.07	11.70	7.94	10.86
Median	15.11	25.79	25.64	24.94	24.84
Min, Max	0.5, 29.6	0.4, 67.1	0.3, 34.5	0.0, 63.2	0.0, 67.1

Source: Applicant's 120-day safety update submission.

N= subjects in studies 20090062, 20120102, 20120103, 20120104 with ≥ 1 dose brodalumab

Due to the design of the clinical trials, most subjects were exposed to the 210 mg Q2W brodalumab at some point. For subjects ever exposed to brodalumab 210 mg, 3135 subjects were exposed to brodalumab 210 mg for ≥12 months and 3515 subjects were exposed to brodalumab (any dose) for ≥12 months. A total of 3741 (91%) subjects were exposed to 210 mg ≥3 months and 3135 (76%) were exposed to 210 mg ≥12 months. Given the cumulative

exposure for subjects receiving the 210 mg Q2W dose by study design, the probability that a subject would have been on the 210 mg Q2W dose at the time of any given AE is high.

8.2.2. Relevant characteristics of the safety population:

The highlighted demographics of the safety population are show in Table 7. Males represent a majority of the subjects (69%) with the majority of the subjects aged 45-64 years old. Previous depression in this population is around 14% across all arms. Baseline depression/suicidality was found to be 15-18%. One-third of subjects had some previous biologic use prior to enrollment in these clinical trials.

Table 11: Baseline Demographic in Safety Population (Phase 2 and Phase 3)

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)
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)
Depression/suicidality	471 (15)	128(15)	112(18)

Source: Agency Biostatistical Review

The relevant characteristics in this safety population is interesting for the reason that CDC vital statistics from 1999-2014 shows increases of suicide rates for both males and females in the age range of 45-64 years of age.⁸

Reviewer's comment: *It is noted that the baseline demographics of the study population is mostly male and in the age group of 45-64 years old. One-third has some history of depression*

⁸ CDC- National Vital Statistics. Suicide Rates in US (1999-2014).

and suicidality.

8.2.3. Adequacy of the safety database:

The safety database presented by the applicant appears to have adequate subject exposure to brodalumab 210mg Q2W dosing. Only 102 subjects were follow-up for the full 5 years previously specified for the long-term clinical trials. Few subjects in the maintenance phase beyond 52-weeks were exposed for an extended period due to the premature end to the trials. This presents a problem for exposure of adverse events that may be rare or infrequent.

8.3. Adequacy of Applicant's Clinical Safety Assessments

8.3.1. Issues Regarding Data Integrity and Submission Quality

The initially submitted BLA package had some issues with access to the study reports for each individual clinical trial. These issues were cleared up with the applicant. The Agency issued several IRs to clarify data packages.

8.3.2. Categorization of Adverse Events

Analyses of identified risks, potential risks and other AEs of interest were performed using searches based on Standardized Medical Dictionary for Regulatory Activities (MedDRA) Queries, Amgen Medical Queries, SOCs, and High Level Group Terms (HLGTs).

Adverse events will also be organized based on the data cut-off period. Tables will include description of Induction stage (first 12 weeks), maintenance phase (up to 52-weeks), and to the end of study (120-day safety update).

8.3.3. Routine Clinical Tests

An extensive laboratory evaluation was completed including neutrophil counts, liver testing, and a full complement of chemistry parameters. The laboratory parameters were evaluated based on CTCAE *version 4.0 or 4.03*.

8.4. Safety Results

8.4.1. Deaths

The observed deaths related to psoriasis trials were updated in the 120-day safety update submitted 4 months after the initial BLA application. A total of 23 treatment-emergent fatal events were reported in brodalumab subjects in the psoriasis subset. New to the report was 8 new treatment-emergent fatalities reported among the brodalumab subset in addition to the 15 reported in the original BLA submission.

Through the end of the psoriasis studies, a total of 23 deaths were reported among patients exposed to brodalumab. The largest category was comprised of 13 cardiovascular-related events, including MI (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. There were 2 deaths, including one due to MI and one due to pancreatic cancer, in the ustekinumab group. The Cardiac Events Committee (CEC) adjudicated MACE events will be discussed in the cardiovascular events sections of this review. The four completed suicides will be discussed in the suicide events sections of this review.

Table 12: All Deaths in Phase 3 Clinical Trials—Psoriasis Subset

Study	Subject ID	Treatment at Time of Event	Sex/Age/Race	Preferred Term	Fist/Last admin date of brodalumab	Start of Event (Day)	Onset from last active dose (days)	Risk Factors
20090062/Psoriasis	96266006016	Overall variable dosing	M/43/AI	Aortic aneurysm rupture	23FEB2010/ 26JUL2010		(b) (6)	DM type II
20120102/Psoriasis	10216004001	210 mg Q2W	M/56/A	Intentional overdose	4DEC2012/ 25FEB2013			Depression and substance abuse
20120102/Psoriasis	10225002005	210 mg Q2W	M/69/W	Esophageal varices hemorrhage	7FEB2013/ 17OCT2013			NASH induced liver cirrhosis; alcohol abuse
20120102/Psoriasis	10248005019	210 mg Q2W	M/58/W	Completed suicide	10APR2013/ 6JAN2014			Financial stress
20120102/Psoriasis	10266009012	Overall variable dosing	M/70/W	Cerebrovascular accident	26NOV2012/ 5AUG2013			Hypertension and arrhythmia, sleep apnea, hypothyroid
20120102/Psoriasis	10266042001	210 mg Q2W	M/74/W	Sudden death	10OCT2012/ 24APR2013			Coronary bypass surgery, obesity, hyper cholesterol, HTN, DM
20120102/Psoriasis	10225002010	210 mg Q2W	M/52/W	Cardiac arrest	14FEB2013/ 14AUG2014			Smoker, hyperlipidemia
20120102/Psoriasis	10266017001	210 mg Q2W	M/55/W	Myocardial infarction	8MAY2013/ 3DEC2014			Pneumonia, septic shock, smoker, high cholesterol
20120103/Psoriasis	10311001011	210 mg Q2W	M/38/W	Cerebral infarction	8MAR2013/ 14MAY2013		(b) (6)	Upper GI hemorrhage, alcohol abuse
20120103/Psoriasis	10311005001	210 mg Q2W after ustekinumab	M/56/W	Pulmonary embolism	6May2014/ 21OCT2014			Pulmonary embolism, HTN, CHF, COPD

20120103/Psoriasis	10348009033	Overall variable dosing	M/60/W	Myocardial infarction	4JUN2013/7OCT2014 (514)	(b) (6)	DM2, HTN
20120103/Psoriasis	10366026003	210 mg Q2W	M/54/W	Completed suicide	23OCT2012/27JAN2015		depression
20120103/Psoriasis	1036603815	Overall variable dosing	M/44/W	Acute myocardial infarction	1MAR2013/17JAN2015		HTN, hyper cholesterol, cocaine user
20120103/Psoriasis	10366022014	Overall variable dosing	M/62/W	Accidental death	4FEB2013/26/MAY2015		Multi-vehicle accident
20120104/Psoriasis	10466071010	Overall variable dosing	M/50/W	Accidental death	27Feb2013/19JUN2013		Motor vehicular accident
20120104/Psoriasis	10448004011	Overall variable dosing	M/63/W	Myocardial infarction	18FEB2013/4MAY2015		Old MI date unknown

Source: Reviewer's analysis of applicant's submission

8.4.2. Serious Adverse Events

The exposure-adjusted rates of SAEs in the 120-day safety update will be discussed. The SOCs with the highest exposure adjusted serious AE rates (per 100 subject years) in the all-brodalumab group were Infections and Infestations (1.1); Cardiac Disorders (0.9); and Injury, Poisoning and Procedural Complications (0.9).

Table 13: Exposure-adjusted rates of Serious Adverse Events in the All-Brodalumab group from first dose through 120-day safety update end of study—Psoriasis Subset

Preferred Term	Brodalumab				
	210 mg Q2W after ustekinumab (subj-yr=715.2) (N= 567) n (r)	Subjects With Brodalumab Exposure Only			All (Subj-yr=8655.0) (N= 4464) n (r)
		Overall Variable Dosing (Subj-yr =4948.8) (N= 2337) n (r)	Overall 140 mg Q2W (Subj-yr= 448.4) (N=256) n (r)	Overall 210 mg Q2W (Subj-yr= 2542.6) (N= 1304) n (r)	
All treatment-emergent serious adverse events	49 (6.9)	341 (6.9)	43 (9.6)	206 (8.1)	639 (7.4)
Cardiovascular Event (All)	1 (0.1)	37 (0.8)	2 (0.4)	15 (0.5)	55 (0.9)
Myocardial Infarction	0	16 (0.3)	1 (0.2)	6 (0.2)	23 (0.3)
Acute myocardial infarction	0	4 (0.1)	0	2 (0.1)	6 (0.1)
Angina unstable	0	3 (0.1)	1 (0.2)	2 (0.1)	6 (0.1)
Angina pectoris	0	5 (0.1)	0	0	5 (0.1)
Atrial fibrillation	1 (0.1)	3 (0.1)	0	1 (0.0)	5 (0.1)
Cardiac failure congestive	0	2 (0.0)	0	3 (0.1)	5 (0.1)
syncope	0	4 (0.1)	0	1 (0.0)	5 (0.1)
Cerebrovascular (All)	0	9 (0.2)	0	2 (0.1)	11 (0.2)
Cerebrovascular Accident	0	4 (0.1)	0	2 (0.1)	6 (0.1)
Ischemic stroke	0	5 (0.1)	0	0	5 (0.1)
SIB (All)	4 (0.6)	12 (0.3)	4 (0.9)	10 (0.4)	30 (0.3)
Suicide attempt	2 (0.3)	2 (0.0)	0	3 (0.1)	7 (0.1)
Suicidal ideation	0	6 (0.1)	0	6 (0.2)	12 (0.1)
Depression	2 (0.3)	4 (0.1)	4 (0.9)	1 (0.0)	11 (0.1)
Infections (All)	1 (0.1)	30 (0.6)	2 (0.4)	15 (0.6)	48 (0.7)
Pneumonia	0	5 (0.1)	1 (0.2)	4 (0.2)	10 (0.1)
Appendicitis	0	5 (0.1)	0	3 (0.1)	8 (0.1)
Cellulitis	1 (0.1)	7 (0.1)	0	5 (0.2)	13 (0.2)
Osteoarthritis	0	5 (0.1)	1 (0.2)	0	6 (0.1)
UTI	0	4 (0.1)	0	2 (0.1)	6 (0.1)
Cholecystitis	0	4 (0.1)	0	1 (0.0)	5 (0.1)
Others					
COPD	2 (0.3)	3 (0.1)	0	4 (0.2)	9 (0.1)
Nephrolithiasis	0	7 (0.1)	1 (0.2)	0	8 (0.1)
Cholelithiasis	1 (0.1)	5 (0.1)	0	4 (0.2)	10 (0.1)
Road traffic accident	0	2 (0.0)	0	3 (0.1)	5 (0.1)

Source: Reviewer analysis of safety data from 120-day safety update. MedDRA version 18.1

N= subjects in study 062/102/103/104

Multiple occurrences of the same event for a subject are counted as multiple events.

For all Serious AEs, there were no imbalances at Week 12 between brodalumab, ustekinumab,

or 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. The SOCs with the highest exposure-adjusted event rates were Infections and Infestations, Injury, Poisoning, and Procedural Complications, and Cardiac Disorders. Serious AEs at Week 52 were similar between brodalumab and ustekinumab. The preferred terms with the highest exposure-adjusted rates (per 100 patient years) at Week 52 were myocardial infarction (0.3 all-brodalumab group, 0.2 ustekinumab), cellulitis (0.2 all-brodalumab, 0.2 ustekinumab), and cholelithiasis (0.2 all-brodalumab, 0.0 ustekinumab). The rates of these events do not increase in the long term.

8.4.3. Dropouts and/or Discontinuations Due to Adverse Effects

In the safety review of the 120-day safety update, the SOC of Psychiatric Disorders had the highest overall exposure-adjusted rate of AEs leading to investigational product discontinuation. The most common PTs within the SOC were depression and suicide ideation. A comparison of the AEs leading to discontinuation from investigational product for the induction period of first 12-weeks is in the table below.

Table 14: Subject Incidence of AE leading to study drug discontinuation and/or study discontinuation by SOC – Induction period (12-weeks) – Psoriasis subset

System Organ Class	Placebo (N=879) n (%)	Ustekinumab (N=613) n (%)	Brodalumab ALL 140mg/210mg (N=3066) n (%)
Number of subjects reporting adverse events leading to investigation product discontinuation	8 (0.9)	6 (1.0)	34 (1.1)
Number of subjects reporting adverse events leading to study discontinuation	5 (0.6)	3 (0.5)	28 (0.9)
Skin and subcutaneous tissue disorders	2 (0.2)	0	5 (0.2)
Gastrointestinal disorders	0	0	5 (0.2)
Infections and infestations	1 (0.1)	0	5 (0.2)
Cardiac disorders	0	0	4 (0.1)
Musculoskeletal and connective tissue disorders	0	0	4 (0.1)
Investigations	0	1 (0.2)	2 (0.1)
Neoplasms benign, malignant and unspecified	0	1 (0.2)	2 (0.1)
General disorders and admin site conditions	1 (0.1)	1 (0.2)	1 (<0.1)
Blood and lymphatic system disorders	1 (0.1)	0	1 (<0.1)
Nervous system disorders	0	0	1 (<0.1)
Renal and urinary disorders	0	0	1 (<0.1)

Source: Module 5.3.5.3, ISS Table 14-6.4.2

N subjects in studies 062/102/103/104 with ≥ 1 dose of investigation product

As described by the incidence rate of these events, most were rare and did not affect the safety profile of the product in the induction phase.

8.4.4. Significant Adverse Events

The significant adverse events are regarding suicidality and the cardiovascular MACE. These safety issues will be discussed in section 8.5 in detail. Other significant events of interest include neutropenia, development of Crohn’s disease, malignancies, and increased infections.

Table 15: Exposure-adjusted event rates (per 100 subject-years) for events of interest through week 52 – to end of study (120-day safety update) – Psoriasis subset

Identified Risk	Maintenance Phase (52 weeks)		Data cutoff date	First dose through 120-day safety update (end-of-study)
	Ustekinumab (subj-yr =494.7) (N= 613) n (r)	All-brodalumab (Subj-yr= 3445.5) (N=4019) n (r)	All-brodalumab (Subj-yr= 5448.8) (N=4461) n (r)	All-brodalumab (Subj-yr= 8655.0) (N=4464) n (r)
Crohn’s disease	0	4 (0.1)	7 (0.1)	12 (0.1)
Infections SOC	584 (118.1)	3950 (114.6)	5539 (101.7)	7759 (89.6)
Neutropenia	12 (2.4)	79 (2.3)	100 (1.8)	104 (1.2)
Ischemic cerebrovascular disease	1 (0.2)	7 (0.2)	12 (0.2)	21 (0.2)
Ischemic Heart Disease	5 (1.0)	40 (1.2)	56 (1.0)	85 (1.0)
Malignancies	13 (2.6)	30 (0.9)	44 (0.8)	43 (0.5)

Source: adapted from Table 13, 120-day Safety Update report.

Neutropenia

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. Decreased circulating neutrophils have been observed in IL-17RA-deficient mice, despite elevated circulating IL-17A levels, due to reduced G-CSF production, mainly in

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non-hematopoietic cells.

In the induction phase (12 weeks) of the clinical trials, incidence rates for AEs due to neutropenia were highest in the brodalumab 210 mg Q2W dose group (1.0%) compared with the brodalumab 140 mg Q2W (0.7%), ustekinumab (0.8%), and placebo (0.5%). The most frequent event was neutropenia (0.7% in 210 mg Q2W and 0% in placebo). Only one event of aplastic anemia was reported and in a placebo subjects. Most subjects had absolute neutrophil count (ANC) of grade 0 (CTCAE version 4.03) throughout the double-blind treatment period. A dose-dependent decrease in absolute neutrophil count (ANC) were observed in subjects with normal ANC at baseline (6.8% in the brodalumab 210 mg Q2W group, 4.7% in the brodalumab 140 mg Q2W group, 3.3% in the ustekinumab group, and 3.6% in the placebo group).

During the induction period (12 weeks):

- Post baseline ANC decreases of grade 4 ($<0.5 \times 10^9/L$) were reported for 2 subjects in the 140 mg Q2W 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 Q2W group and 3 subjects in the 140 mg Q2W group, compared with 0 placebo or ustekinumab subjects. Of these, 2 subjects in the 210 mg Q2W group and 2 subjects in the 140 mg Q2W 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. No unbalance was seen through the data cutoff for neutropenia, neutrophil count decrease, or abnormal white cell count. Grade 3 or 4 decreases in ANC were observed in 0.4% of subjects in the all-brodalumab group. Most were transient and were not temporally associated with serious infections.

During the maintenance period (up to 52 weeks):

- Decreases in ANC of grade 4 were reported for 4 brodalumab subjects (0.1%) compared with 1 ustekinumab subject (0.2%).
- Post baseline ANC decreases of grade 3 were reported for 0.4% of brodalumab subjects and 0.2% of ustekinumab subjects. The incidences of grade 3 decreases in ANC were similar across brodalumab dose groups. Two subjects discontinued investigational product due to grade 3 decreased absolute neutrophil counts. None of the grade 3 or 4 ANC decreases were associated with a serious infection.

Through week 52 and through the data cutoff, there were 0.1% of brodalumab subjects with a grade 4 decrease, including 3 subjects with variable dosing and 1 subject who received 140 mg Q2W. Two subjects discontinued investigational product due to grade 3 decreases in ANC.

Reviewer’s comment: *Neutropenia was observed in a small number of subjects and was not dose dependent. None of the reduction in ANC observed was associated with a serious infection.*

Infections and Infestations

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. The observed exposure-adjusted event rate of AEs in the Infections and Infestations SOC was 89.6 events per 100 subject-years for the all brodalumab group.

The most frequent events (≥ 4.0 events per 100 subject-years) in the all-brodalumab group were nasopharyngitis (17.5) and upper respiratory tract infection (14.9).

Table 16: Adverse Events in the Infections and Infestations SOC occurring $\geq 1\%$ of subjects in the All-brodalumab group during the initial double-blind period – Psoriasis subset

System Organ Class	Placebo (N=879) n (%)	Ustekinumab (N=613) n (%)	Brodalumab ALL 140mg/210mg (N=3066) n (%)
Infections and infestations SOC	206 (23.4)	153 (25.4)	780 (25.4)
Grade ≥ 2	146 (16.6)	123 (20.1)	587 (19.1)
Grade ≥ 3	3 (0.3)	3 (0.5)	19 (0.6)
Grade ≥ 4	0	0	1 (<0.1)
Nasopharyngitis	61 (6.9)	34 (5.5)	209 (6.8)
Upper respiratory tract infection	56 (6.4)	63 (5.9)	163 (5.3)
Pharyngitis	9 (1.0)	5 (0.8)	39 (1.3)
UTI	8 (0.9)	10 (1.6)	33 (1.1)
Influenza	4 (0.5)	7 (1.1)	32 (1.0)
Bronchitis	12 (1.4)	7 (1.1)	31 (1.0)

Source: Table 14-6.49.1 and 14-6.48.1, ISS
 N= studies 062/102/103/104

Events were coded using CTCAE version 4.3 and MedDRA version 17.1

Overall, through week 52, no meaningful increase in events in the Infections and Infestations SOC was observed in subjects who received brodalumab compared with subjects who received ustekinumab. Most events were of grade 1 or 2 in severity. Individual grade ≥ 3 events reported for subjects in the all-brodalumab and ustekinumab groups occurred at an exposure-adjusted event rate (per 100 subject-years) of ≤ 0.2 , with the exception of cellulitis (0.4 all-brodalumab, 0.2 ustekinumab) and tooth infection (< 0.1 all-brodalumab, 0.4 ustekinumab). Events of grade 4 severity were single occurrences reported for 1 subject each: furuncle (Subject 10435012017; brodalumab 210 mg Q2W constant dose), appendicitis (Subject 10248001038; brodalumab 140 mg Q2W/210 mg Q2W group), sepsis (Subject 10466025006; brodalumab 210 mg Q2W/140 mg Q2W/210 mg Q2W), cholecystitis infective (Subject 10466090013; brodalumab 210 mg Q2W constant dose), and septic shock (Subject 96216004002; brodalumab 210 mg Q2W).

Table 17: Adverse Events in Infections and Infestations SOC with exposure-adjusted rates ≥ 4 per 100 subject-years for all brodalumab group (52 weeks) –Psoriasis subset

Preferred Term	Brodalumab						
	Ustekinumab (Subj-yr = 494.7) (N=613) n (r)	Variable Dose			Constant Dose		
		210 mg Q2W After Ustekinumab (Subj-yr = 75.5) (N=119) n (r)	Mixed Dosing (Subj-yr = 1202.4) (N=1312) n (r)	140 mg Q2W/ 210 mg Q2W (Subj-yr = 910.4) (N=973) n (r)	140 mg Q2W (Subj-yr = 215.3) (N=280) n (r)	210 mg Q2W (Subj-yr = 1042.0) (N=1335) n (r)	All (Subj-yr = 3445.5) (N=4019) n (r)
Adverse events in the infections and infestations SOC	584 (118.1)	80 (106.0)	1410 (117.3)	1025 (112.6)	185 (85.9)	1250 (120.0)	3950 (114.6)
Nasopharyngitis	115 (23.2)	18 (23.8)	266 (22.1)	243 (26.7)	49 (22.8)	225 (21.6)	801 (23.2)
Upper respiratory tract infection	125 (25.3)	14 (18.5)	253 (21.0)	158 (17.4)	29 (13.5)	208 (20.0)	662 (19.2)
Urinary tract infection	33 (6.7)	2 (2.6)	46 (3.8)	42 (4.6)	7 (3.3)	51 (4.9)	148 (4.3)
Sinusitis	20 (4.0)	6 (7.9)	62 (5.2)	38 (4.2)	3 (1.4)	42 (4.0)	151 (4.4)
Bronchitis	24 (4.9)	2 (2.6)	50 (4.2)	29 (3.2)	11 (5.1)	45 (4.3)	137 (4.0)

Abbreviations: N subjects in Studies 20090062/20090403, 20120102, 20120103, and 20120104 with ≥ 1 dose of active investigational product; n number of adverse events; r exposure-adjusted event rate per 100 subject-years (n/subj-yr*100); Subj-yr =Total subject-years of exposure through week 52. Treatment groups are as planned treatment; 140/210=140 mg Q2W and 210 mg Q2W; Mixed Dosing=140 mg Q4W or Q8W, planned placebo treatment in study, or dosing gaps between studies; Ustekinumab subjects rescued at week 16, are in "Ustekinumab" until first dose of brodalumab, then in "210 mg Q2W After Ustekinumab"

Multiple occurrences of the same event for a subject are counted as multiple events. MedDRA v. 17.1
 Source: Module 5.3.5.3, ISS Table 14-6.48.3

Through the data cutoff, the exposure-adjusted event rate of AEs in the Infections and Infestations SOC was 101.7 events per 100 subject-years for the all-brodalumab group. The most frequent events (≥ 4.0 events per 100 subject-years) in the all-brodalumab group were nasopharyngitis, upper respiratory tract infection, and sinusitis.

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For serious adverse events in the infections and infestations SOC, the incidence rates through week 12 was 0.5% for brodalumab 210 mg Q2W, 0.5% brodalumab 140 mg Q2W, 0.3% for ustekinumab, and 0.2% for placebo.

In the maintenance phase of the clinical trials (52 weeks), the exposure-adjusted event rates (per 100 subject-years) of serious AEs in the Infections and Infestations SOC were similarly low (1.3 all-brodalumab, 1.0 ustekinumab). Within the all-brodalumab group, exposure adjusted event rates were similar across the different dose groups. The most common serious infection AEs were cellulitis for the all-brodalumab group and cellulitis, diverticulitis, perichondritis, tick-borne viral encephalitis, and tubo-ovarian abscess for ustekinumab group. Appendicitis, urinary tract infection, diverticulitis, gastroenteritis, pneumonia, pyelonephritis acute, and sepsis occurred at a rate of 0.1 per 100 subject-years in the all-brodalumab group; with the exception of diverticulitis, these events were not reported for subjects in the ustekinumab group.

Two subjects reported a serious opportunistic infection:

- Grade 3: Cryptococcal meningitis in a 39-year old white male.
- Grade 2: Coccidioidomycosis in a 52-year old white male.

The subjects described were also the serious fungal infections that were reported through the 52-week period.

Reviewer's comment: *IL-17 signaling is postulated to play a role in protection against other fungi, but while administration of an IL-17A neutralizing antibody blunted pulmonary fungal clearance and inflammatory cell recruitment, it did not promote progressive infection. Based on the few serious cases of fungal infections, a causal association seems unlikely but cannot be ruled out.*

Subjects with Grade 4 serious infections:

- Appendicitis in a 41-year old white man.
- Sepsis with respiratory failure in a 46-year old white male; suspected narcotic overdose.
- Cholecystitis in a 39-year old white woman.
- Furuncle in a 29-year old white male.
- Septic shock in a 25-year old white woman who developed streptococcal necrotizing fasciitis complicated by sepsis.

All subjects with grade 4 serious infections received brodalumab 210 mg Q2W.

Candida infections were the most frequently reported fungal infections and were mostly grade 1 or 2 in severity; 1 grade 3 each of oral candidiasis and candida infection was reported. Onset of candida typically occurred after ≥ 90 days of treatment and approximately 25% of all subjects who had candida infections had more than 1 event of candida. One event of esophageal

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candidiasis led to discontinuation of investigational product and study in a 58 year old woman (Subject 10366059031); no other candida infection led to study discontinuation.

Exposure-infection relationship did not seem to be evident from the data presented. For the maintenance period, there was no clear trend of increasing AE rate with increasing brodalumab concentrations for the category of serious infections, candida infections, or viral infections. Although the causation association may be there, the data does not provide a clear relationship.

Reviewer's comment: *Based on biologic plausibility, a higher rate of events in the brodalumab treatment groups compared with placebo and ustekinumab, and a dose-response trend within brodalumab groups, infections are proposed as an important identified risk. Candida infections and tinea pedis, specifically, are considered ADRs. Language has been proposed in the warnings and precautions section of the label to communicate the potential for this risk.*

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

The DEPI-I review summarized that the rate of serious infections observed with brodalumab treatment was similar to rates for the other psoriasis biologics. However, a causal relationship

of brodalumab therapy to infection risk may be presumed, as a property shared with other immunosuppressive therapies for psoriasis.

Table 18: Rates of Serious Infections with Exposure to Specific Products in Psoriasis Trials

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

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

Crohn's Disease

Brodalumab was evaluated in 2 studies of subjects with Crohn's disease, both of which were terminated early due to lack of efficacy, and safety concerns related to worsening of disease. Because worsening of Crohn's disease in subjects with a history or active Crohn's disease is an important identified risk for brodalumab, subjects with a known history of Crohn's disease were

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excluded from brodalumab psoriasis clinical studies.

In the placebo-controlled phase of the clinical trials, only 1 subject in the placebo group had and AE related to Crohn's disease. In the maintenance phase of the clinical trials (52-weeks), the exposure-adjusted event rate of AEs for Crohn's disease was 0.1 per 100 subject-years for the all-brodalumab group; a total of 4 AEs for Crohn's, all of which occurred in the brodalumab dose groups (enteritis =3 and Crohn's=1). Through the data cutoff, the exposure-adjusted event rate of AEs of Crohn's disease in the all-brodalumab group was 0.1 per 100 subject-years. Three additional events of enteritis were reported through the data cutoff compared with through week 52.

A single event of new onset on brodalumab 210 mg Q2W occurred in a 37 year-old white male on study day 209 (subject 10325002005). This subject was discontinued from the study.

Reviewer's comment: Given the observed worsening of symptoms in subjects with a history or active Crohn's disease in 2 studies of subjects with Crohn's disease, Crohn's disease in patients with active Crohn's disease is specified as an important identified risk and Crohn's disease is a contraindication in the label.

8.4.5. Treatment Emergent Adverse Events and Adverse Reactions

Common adverse events were capture in the induction phase (12 weeks) to describe the safety profile of the product. These events were consistent in the maintenance phase and the long-term phase of the development plan.

Table 19: Adverse Drug Reactions during Induction Phase (12 weeks) – Integrated Safety Analysis Set – Psoriasis subset

Preferred Term or Search Strategy (AMQ/HLT)	CIOMS Frequency	Brodalumab							
		Placebo (N=879)		Ustekinumab (N=613)		140 mg Q2W (N=1491)		210 mg Q2W (N=1496)	
		Any Grade n (%)	Grade ≥3 n (%)	Any Grade n (%)	Grade ≥3 n (%)	Any Grade n (%)	Grade ≥3 n (%)	Any Grade n (%)	Grade ≥3 n (%)
Headache	Common	31 (3.5)	1 (0.1)	23 (3.8)	0 (0.0)	81 (5.4)	2 (0.1)	64 (4.3)	0 (0.0)
Arthralgia	Common	29 (3.3)	0 (0.0)	15 (2.4)	1 (0.2)	71 (4.8)	3 (0.2)	71 (4.7)	3 (0.2)
Fatigue	Common	10 (1.1)	0 (0.0)	16 (2.6)	0 (0.0)	34 (2.3)	1 (0.1)	39 (2.6)	0 (0.0)
Oropharyngeal pain	Common	10 (1.1)	0 (0.0)	8 (1.3)	0 (0.0)	32 (2.1)	0 (0.0)	31 (2.1)	1 (0.1)
Diarrhoea	Common	10 (1.1)	0 (0.0)	5 (0.8)	0 (0.0)	25 (1.7)	1 (0.1)	33 (2.2)	1 (0.1)
Nausea	Common	10 (1.1)	0 (0.0)	6 (1.0)	0 (0.0)	26 (1.7)	0 (0.0)	28 (1.9)	0 (0.0)
Myalgia	Common	3 (0.3)	0 (0.0)	4 (0.7)	0 (0.0)	20 (1.3)	0 (0.0)	26 (1.7)	0 (0.0)
Influenza	Common	4 (0.5)	0 (0.0)	7 (1.1)	0 (0.0)	13 (0.9)	0 (0.0)	19 (1.3)	0 (0.0)
Conjunctivitis	Uncommon	1 (0.1)	0 (0.0)	2 (0.3)	0 (0.0)	11 (0.7)	0 (0.0)	11 (0.7)	0 (0.0)
Injection site reactions (AMQ)	Common	11 (1.3)	0 (0.0)	12 (2.0)	0 (0.0)	25 (1.7)	0 (0.0)	23 (1.5)	0 (0.0)
Neutropenia (AMQ)	Common	4 (0.5)	0 (0.0)	5 (0.8)	0 (0.0)	11 (0.7)	4 (0.3)	15 (1.0)	5 (0.3)
Candida infections (HLT)	Uncommon	2 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	9 (0.6)	0 (0.0)	14 (0.9)	0 (0.0)
Tinea infections (HLT)	Common	2 (0.2)	0 (0.0)	3 (0.5)	0 (0.0)	4 (0.3)	0 (0.0)	15 (1.0)	0 (0.0)

Abbreviations: AMQ Amgen MedDRA Queries; CIOMS Council for International Organizations of Medical Sciences; HLT High-level term; N subjects in Studies 20090062, 20120102, 20120103, and 20120104 with ≥1 dose of investigational product; n number of subjects reporting ≥1 occurrence of an adverse event through week 12; %=n/N*100.

CTCAE v. 4.0 or 4.03; MedDRA v. 17.1

Treatment groups are defined as planned (randomized) treatment.

The classification of Very common, Common, and Uncommon events is based on cutoff percentages that were applied to the higher percentage seen in the 2 brodalumab dosing groups in the any Grade column (Very Common: ≥10%; Common: 1% to <10%; Uncommon: < 1%).

Source: Program: /userdata/stat/amg827/meta/bla_2015_pso/analysis/css/prod/adhoc/t-adr-pso.sas

Output: t14b-06-069-001-adr-db-pso.rtf (Date Generated: 30APR2015:14:16) Source Data: adam.adsl, adam.adae.

Note that the most common AE were headaches and arthralgia. Most were mild and resolved.

8.4.6. Laboratory Findings

The majority of subjects in each treatment group had laboratory parameters with baseline

grades of 0 (CTCAE version 4.03) and remained at this grade post baseline, except for glucose for which baseline and/or post baseline increases of grade 0 or 1 occurred at similar frequencies. Limited grade 3 or 4 increases or decreases were reported during the brodalumab studies and occurred at similar incidences across treatment groups. In general, changes in laboratory parameters were not clinically relevant.

8.4.7. Vital Signs

Blood pressure, heart rate, respiratory rate, and temperature were measured at predefined time points according to the protocol assessments. No clinically noticeable changes in the treatment arms versus placebo were appreciated.

8.4.8. Electrocardiograms (ECGs)

There appeared to be no relationship between QTcF values and serum brodalumab levels over a broad range of brodalumab serum concentrations (<50 to >300,000 ng/mL) with multiple QTcF data points collected at or near maximal brodalumab serum concentrations. At screening, pre-dose, and at predefined on-treatment and follow-up visits, 12-lead ECGs were performed and reported ventricular rate and including PR, QRS, QT, and QTc intervals were performed. No subjects had a QTcB (Bazett corrected QT interval) or QTcF interval >500 msec or a change from baseline >60 msec.

A through QT/QTc study was not performed because monoclonal antibodies are unlikely to interact with ion channels due to their large size and high target specificity.

Reviewer's comment: The Agency agreed with the sponsor; however, a waiver was not requested for brodalumab and QT/QTc study.

8.4.9. QT

Not applicable.

8.4.10. 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. However, brodalumab trough concentrations in ADA positive subjects appear to fall within the range of those observed in study 20120102. Note that the variability of brodalumab trough concentrations is large which may be attributable to the PK nonlinearity.

While a definitive determination of the immunogenicity impacts on PK or efficacy could not be made because of the large variability in brodalumab trough concentrations and a small number of subjects who developed ADA in psoriasis clinical trials, whether the numerically lower response rate in ADA positive subjects observed at Week 52 will continue to decrease after a longer term treatment remains to be evaluated.

8.5. Analysis of Submission-Specific Safety Issues

Two specific safety issues were germane to this submission. The first was the suicide complete and ideation/attempt (SIB) rates that were revealed during the Phase 3 clinical trials. The second safety issue is the cardiovascular events that stems from the mechanism of action (MOA) of the receptor antagonist increase the peripheral cytokine leading to possible increase inflammatory factors. In this section, these issues will be discussed in detail.

8.5.1. Suicide Ideation and Behavior (SIB)

SIB encompasses the terms completed suicide, suicide attempt, suicide behavior and suicide ideation. The review of SIB events began in late 2013. The first report of a completed suicide was submitted to the Agency on March 30, 2013. A subsequent report for potential risk of suicide behavior and ideation was submitted on February 7, 2014. In a teleconference later held between the sponsor and the Agency, the sponsor reported that as of January 14, 2014, an estimated 5041 subjects received at least one dose of brodalumab in all clinical trials. The report described 11 individual suicide behavior and ideation events, 4 completed suicides, and 3 deaths from unknown cause from October 8, 2010 through February 3, 2014. All subjects were unblinded and found to be on active drug product, which included 2 subjects exhibiting SIB in the ustekinumab arm.

Based on the unbalanced safety signal, the agreement was to implement the following:

- Update Investigator's Brochure and Informed Consent Documents.
- Amend ongoing 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

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- 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 electronic CSSRS will be 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 will have investigational product permanently discontinued and will immediately be referred to a mental health professional.

The PHQ-8 will be administered at every visit to identify at-risk subjects with severe depression (defined as a total score ≥ 10), who will have investigational product permanently discontinued and will be immediately referred to a mental health professional.

- The sponsor will provide a summary report every 6 months regarding depression, suicidal ideation, and behavior using expanded search methodology outlined in the submission.
- The sponsor also agreed that the brodalumab clinical trials independent Data Monitoring Committee will provide paper progress reports to the Agency directly.
- The sponsor will perform a quantitative analysis of suicide signals, including analyses of specific and related events in comparison to the control groups, including absolute (%) and exposure-based (person-time) comparisons.

On May 13, 2015, after the initial pre-submission meeting, the Agency met with Amgen to discuss the safety signals of completed suicides and SIB observed in the clinical development program for brodalumab. A recommendation was made to the sponsor to further evaluate this risk and be prepared to comprehensively address this safety concern at the time of BLA submission. On May 29, 2015, Amgen announced they were no longer co-developing brodalumab and initiated a plan for early termination of all ongoing clinical trials across all indications. On November 16, 2016, AstraZeneca submitted BLA 761032 for the treatment of moderate to severe plaque psoriasis in adult patients who are candidates for systemic therapy or phototherapy. During the review of the product application, AstraZeneca informed the Agency that it transferred all rights and ownership to Valeant Pharmaceuticals North America LLC.

Once the application was submitted under the BLA, The Division of Dermatology and Dental Products reviewing this application sought consultation from the various specialties in the Agency to help review the SIB signal.

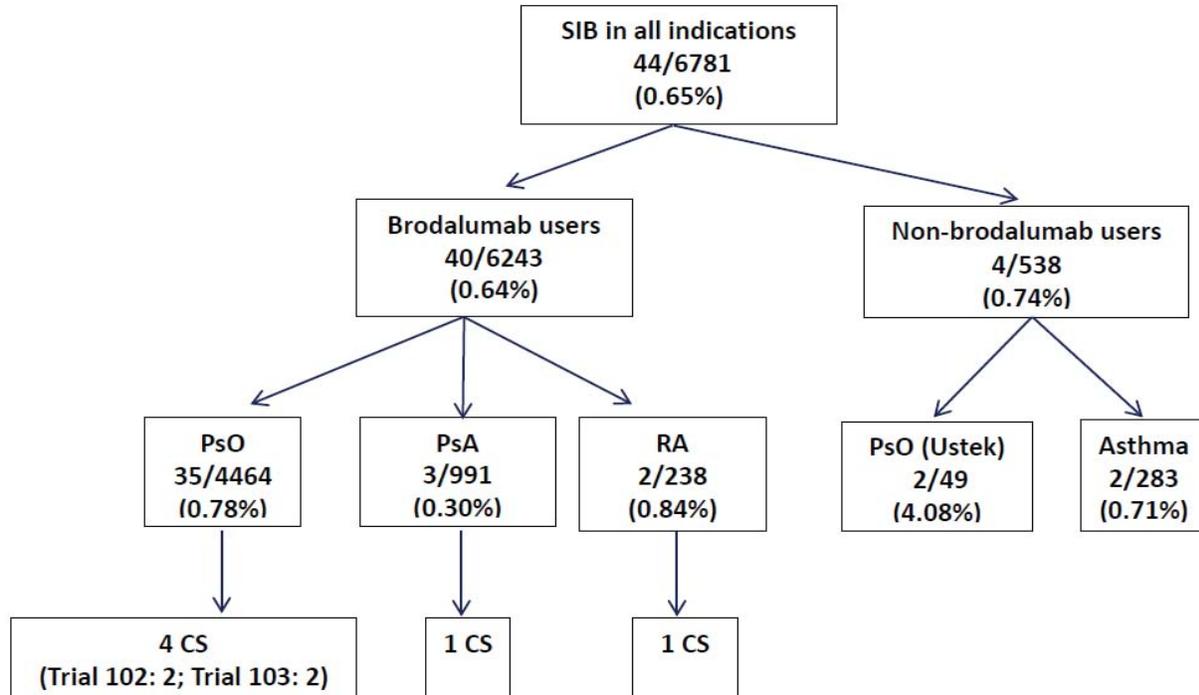
The Division of Dermatology and Dental Product requested the Division of Biostatistics – VII (DB7) to analyze the data submitted for the SIB. Analyses were undertaken to evaluate the

incidence of and risk factors for SIB in the brodalumab development program.

In all brodalumab programs, a total of six completed suicides occurred, of which one was adjudicated as indeterminate. Four completed suicides were adjudicated in the psoriasis (PsO) program, one in rheumatoid arthritis (RA) and one in psoriatic arthritis (PsA) programs. The four subjects in the psoriasis program were males (39M, 56M, 56M, and 58M). The subject in the PsA program was a 57 year-old male and the subject in the RA program was a 36 year-old female. All suicides occurred in subjects exposed to brodalumab. It should be noted that by the design of the programs, the exposure time of brodalumab was much greater than that of the active control and placebo.

DB7 analyzed suicidal ideation and behavior (SIB) using the 120-day safety update dataset. The flow chart (Figure 9) illustrates the number and proportion of subjects who experienced at least one SIB event in the program for PsO and in programs for other indications such as PsA, RA, Crohn’s disease and asthma. In total, 44 of 6781 subjects experienced SIB. Among brodalumab users, we identified 40 SIBs, including 35 SIBs in PsO trials, 3 in the PsA trial and 2 in the RA trial.

Figure 21: Distribution of suicidal ideation and behavior in All-brodalumab trials



Source: DB7 reviewer analysis
 CS: completed suicide; PsA: psoriatic arthritis; RA: rheumatoid arthritis

The safety population for this SIB analysis included subjects from four PsO trials: one Phase 2

trial, and three Phase 3 trials. Table 16 summarizes selected baseline demographics and characteristics by original treatment assignment.

Table 20: Baseline demographic of the 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)

* Depression was determined by medical history of depression and usage of antidepressant at baseline
 Source: DB7 Reviewer's analysis

We estimated the number (%) of subjects who experienced an SIB and the follow-up time-adjusted incidence rate in the psoriasis (PsO) safety population by study phase: induction phase (first 12 weeks), active-controlled phase (first 52 weeks), and from randomization to end of follow-up. Because the PsO program was not designed, and consequently not powered, to compare the treatment arms with respect to SIB events, we did not conduct statistical testing. During the 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 comparator arms.

At the end of the induction period, the majority of placebo subjects and some ustekinumab

subjects received brodalumab. During the 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).

Table 21: 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

Table 18 presents the number (%) of subjects with SIB events and follow-up time adjusted incidence rates from randomization to end of follow-up. In total, 35 SIB events occurred in the brodalumab arm (0.78%; 95% CI: 0.63–1.25) and the follow-up time adjusted incidence rate was 0.38 per 100 subject-years (95% CI: 0.27–0.53).

Table 22: SIB incidence and time-adjusted rates in PsO trials from Day 1 to end-of-follow-up

SIB	Brodalumab n = 3897	Brod after Ustek n = 567	Ustekinumab n = 49	Placebo n = 45
Number (%)	28 (0.72)	7 (1.23)	2 (4.08)	0
Follow-up time	8395.8	778.1	23.1	0
Incidence rate*	0.33	0.9	8.66	0
Brodalumab + Brodalumab after Ustekinumab n = 4464				
Number (%; 95% CI)	35 (0.78; 0.63–1.25)			
Follow-up time	9173.9			
Incidence rate*	0.38 (0.27–0.53)			

*per 100 subjects years

We conducted a subgroup analysis to estimate the incidence rate of SIB events among brodalumab users by the baseline depression status and suicidality status (Table 19).

Baseline depression was determined by medical history of depression and usage of antidepressants. Brodalumab users with a history of depression had an approximately seven-fold increase in SIB incidence rate than users without a history.

Because suicidality assessment was implemented following the initiation of the Phase 3 psoriasis trials, baseline suicidality was determined by CSSRS, and through an additional “since the study start questionnaire.” The sponsor defined suicidality as unknown if the subject had a positive eCSSRS response (i.e., suicidal ideation [score of 4 to 5] and/or behavior) from the “lifetime questionnaire” and a positive score from the “since study start questionnaire” but did not have a medical history of suicidality. Because of the ambiguity of this category, we categorized subjects in the following three ways: original category (yes, no, unknown), treat unknown as yes, and treat unknown as no. Brodalumab users with a history of suicidality had an approximately 12–18 fold increase in SIB incidence rate than users without a history.

Table 23: SIB incidence rate by baseline depression or suicidality

Subgroups	No. of brodalumab users (subject-years) N = 4464	No. of SIB (%)	Incidence rate per 100 subject-years
Depression			
Yes	633 (1201)	18 (3)	1.5
No	3831 (7973)	17 (0)	0.21
Ratio of Yes/No			7.1
Suicidality			
Original categories			
Yes	122 (253)	9 (7)	3.56
No	3835 (8539)	17 (0)	0.2
Unknown	507 (382)	9 (2)	2.36
Ratio of Yes/No			17.8
Unknown as Yes			
Yes	629 (635)	18 (3)	2.83
No	3835 (8539)	17 (0)	0.2
Ratio of Yes/No			14.2
Unknown as No			
Yes	122 (253)	9 (7)	3.56
No	4342 (8921)	26 (1)	0.29
Ratio of Yes/No			12.3

Source: DB7 analysis

The eCSSRS was instituted more than mid-way through the Phase 3 clinical trials after discovery of the suicidality signal. **Table 24** evaluates the first initiation of the eCSSRS and the PHQ-8 tools. The table identified when the eCSSRS was initiated and how many subjects received the assessment in each Phase 3 clinical trial. Only study 103 and 104 had subjects that were screened with the assessment tools. The majority of the subjects in study 102 were past week-52 by the time the tools were implemented.

Table 24: Study Week of first eCSSRS Assessment - March 2015 Data Cutoff - Integrated Safety Analysis Set - Phase 3 Psoriasis Subset

	Study 102 (N=536) n (%)	Study 103 (N=1549) n (%)	Study 104 (N=1598) n (%)
Week 28 to <40	0	19 (1.2)	1 (0.1)
Week 40 to <52	0	264 (17.0)	272 (17.0)
Week 52 to <64	0	417 (26.9)	490 (30.7)
Week 64 to <76	76 (14.2)	290 (18.7)	344 (21.5)
Week 76 to <88	260 (48.5)	348 (22.5)	321 (20.1)
Week 88 to <100	189 (35.3)	192 (12.4)	156 (9.8)
Week 100 to <112	11 (2.1)	17 (1.1)	11 (0.7)
Week 112 to <124	0	2 (0.1)	2 (0.1)
Week 124 to <136	0	0	1 (0.1)

N= subjects in studies 102/103/104 with ≥ 1 dose of investigation product and ≥ 1 on-study C-SSRS assessment
 Assessments that were inactivated by the site due to entry error were excluded from the analysis
 N=number of subjects with first C-SSRS assessment at specified study weeks
 %=n/N*100

Using the most severe on-study eCSSRS response in the Phase 3 clinical trials, an evaluation of the severity of response was reviewed. **Table 25** represents a comparison of study 103 and 104 and the severe eCSSRS responses. The analysis reveals that higher numbers of brodalumab subjects had some suicidal ideation or behavior during the study with equal baseline suicidality at the beginning of the study. Although this analysis is limited, it does illustrate that some mechanism is in action for the neuropsychiatric response subjects on brodalumab is experiencing.

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Table 25: eC-SSRS Response through Week 52 - Integrated Safety Analysis Set - Psoriasis Subset trial 103 and 104

Most severe on-study eC-SSRS response	Brodalumab	Ustekinumab	All subjects*
	n (%)	n (%)	n (%)
All subjects (N)	519	114	793
Any suicidal ideation or behavior (≥ 1)	23 (4)	2 (2)	30 (4)
Suicidal behavior only	1 (0)	0 (0)	1 (0)
Suicidal ideation (4-5) or behavior	2 (0)	0 (0)	2 (0)
Baseline suicidality			
No	495	102	748
Any suicidal ideation or behavior (≥ 1)	16 (3)	1 (1)	21 (3)
Suicidal ideation (4-5) or behavior	0	0	0
Yes	17	9	33
Any suicidal ideation or behavior (≥ 1)	3 (18)	1 (11)	5 (15)
Suicidal ideation (4-5) or behavior	1 (6)	0 (0)	1 (3)
Unknown	7	3	12
Any suicidal ideation or behavior (≥ 1)	4 (57)	0 (0)	4 (33)
Suicidal ideation (4-5) or behavior	1 (14)	0 (0)	1 (8)

Source: DB7 review of data submitted

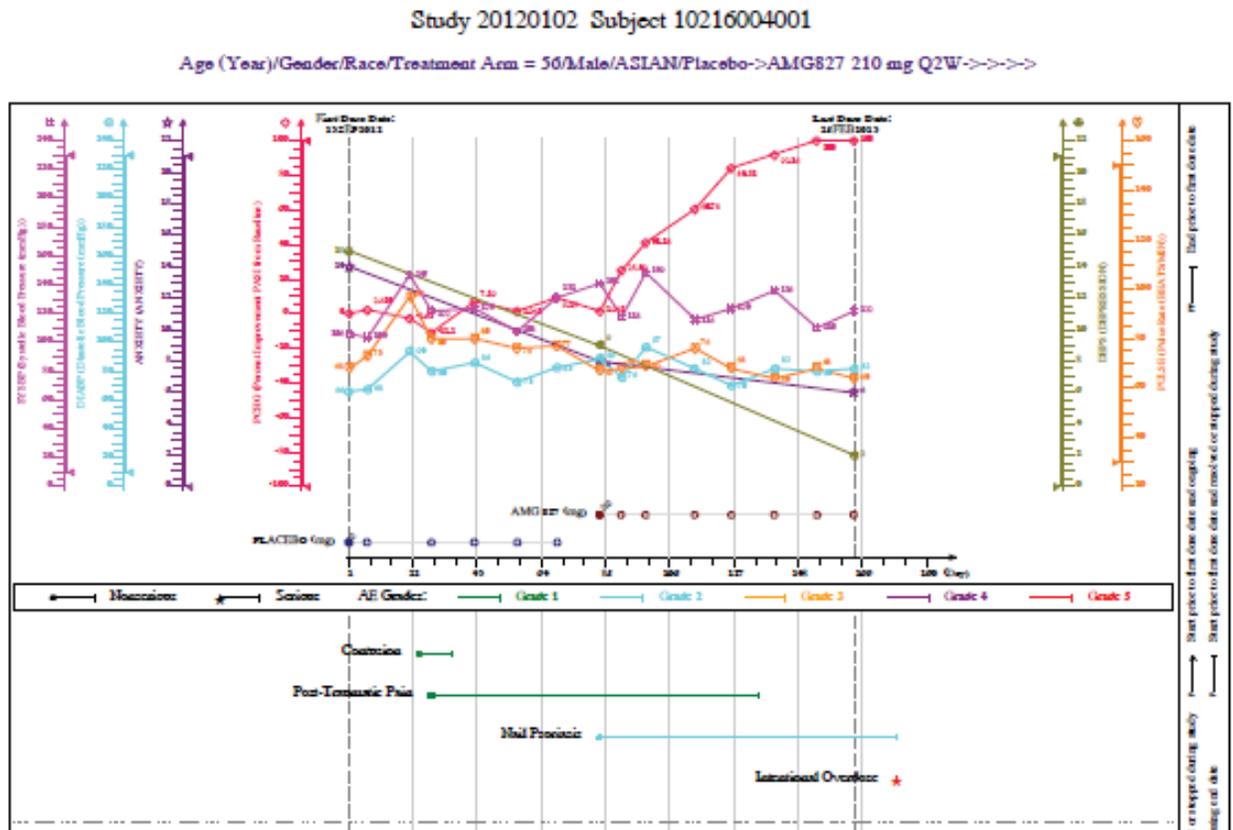
*All subjects included in placebo and brodalumab arm and ustekinumab to brodalumab arm during the first 52 weeks in addition to brodalumab arm and ustekinumab arm

Reviewer's comment: *The limited duration of the placebo-controlled portion of the trial did not provide an adequate comparison between the arms to make any observations. In the extended phase of the active open-label portion of the clinical trials, brodalumab users with a history of suicidality had an approximately 18-fold increase in Sib incidence than users without a history. In this reviewer's opinion, a safety signal exists for completed suicides.*

Using JReview (data analysis tool), this reviewer was able to replicate patient profiles for the 4 completed suicides in the psoriasis program.

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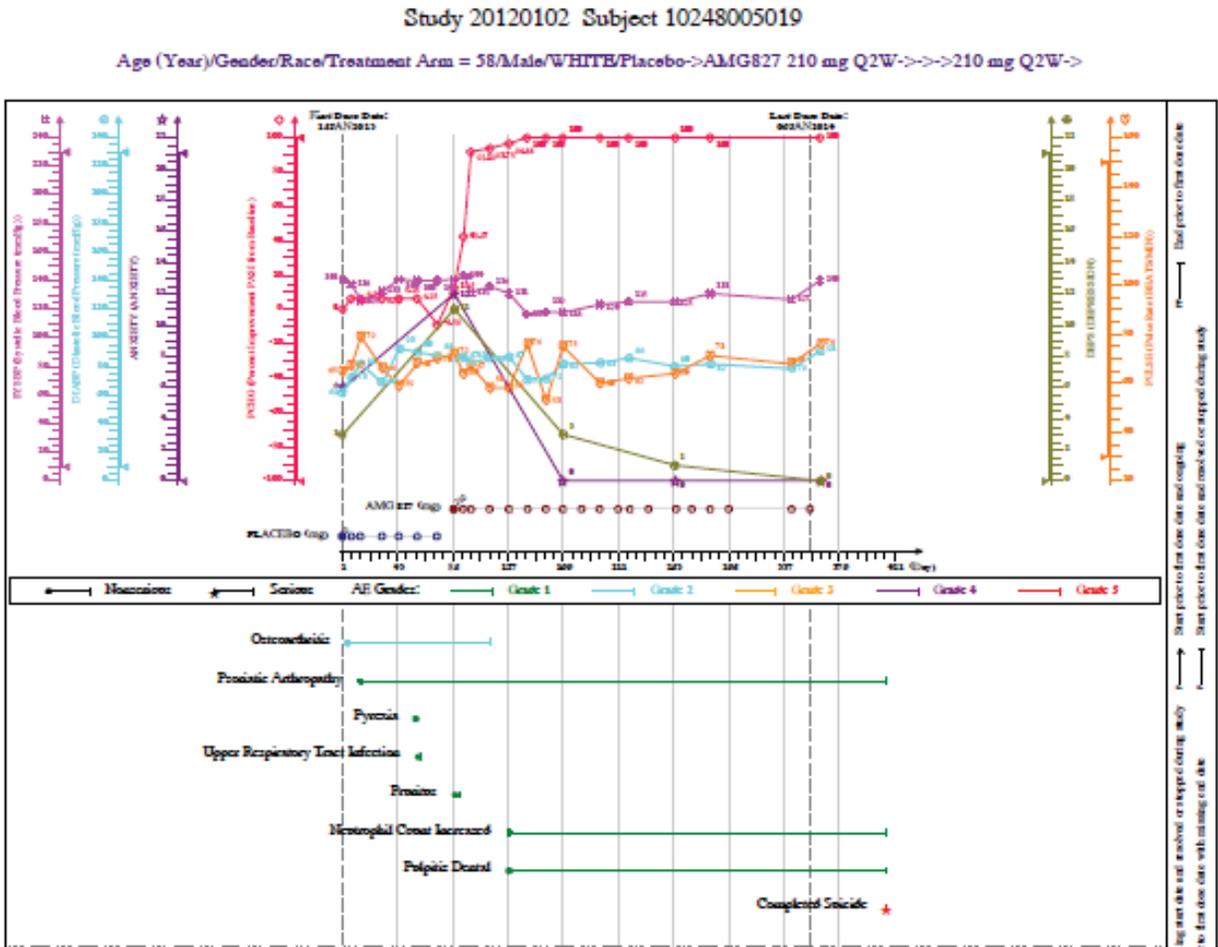
Figure 22: Patient Profile 4001



This first subject is a 56 year-old Asian male who the coroner determined the death as a suicide. Later adjudication showed that this was an indeterminate suicide. The subject's wife stated that he had financial problems and was a drug addict. He was found in his truck after overdose on narcotics.

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Figure 23: Patient Profile 5019

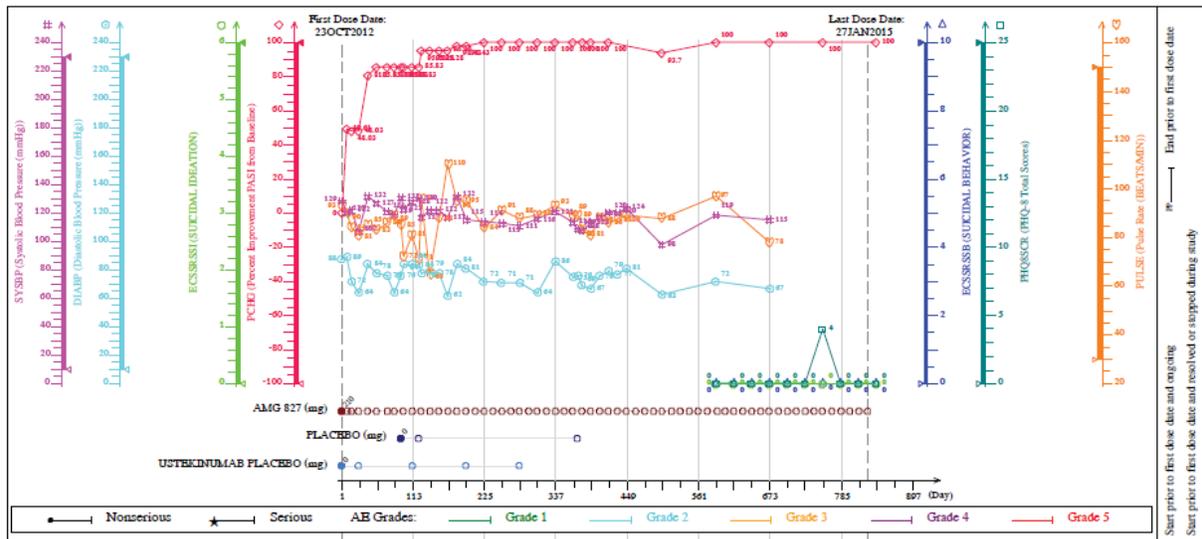


The second subject who completed suicide in study 102 is presented here. This subject was on placebo for the first 12-weeks of the control period and switched to brodalumab 210 mg during the maintenance period. The red line represents the primary endpoint of PASI-75. The subject had very good response once switched to brodalumab. The purple line illustrates the HADS (Hospital Anxiety and Depression Scale); as the subject improved his psoriasis, the anxiety scale dropped.

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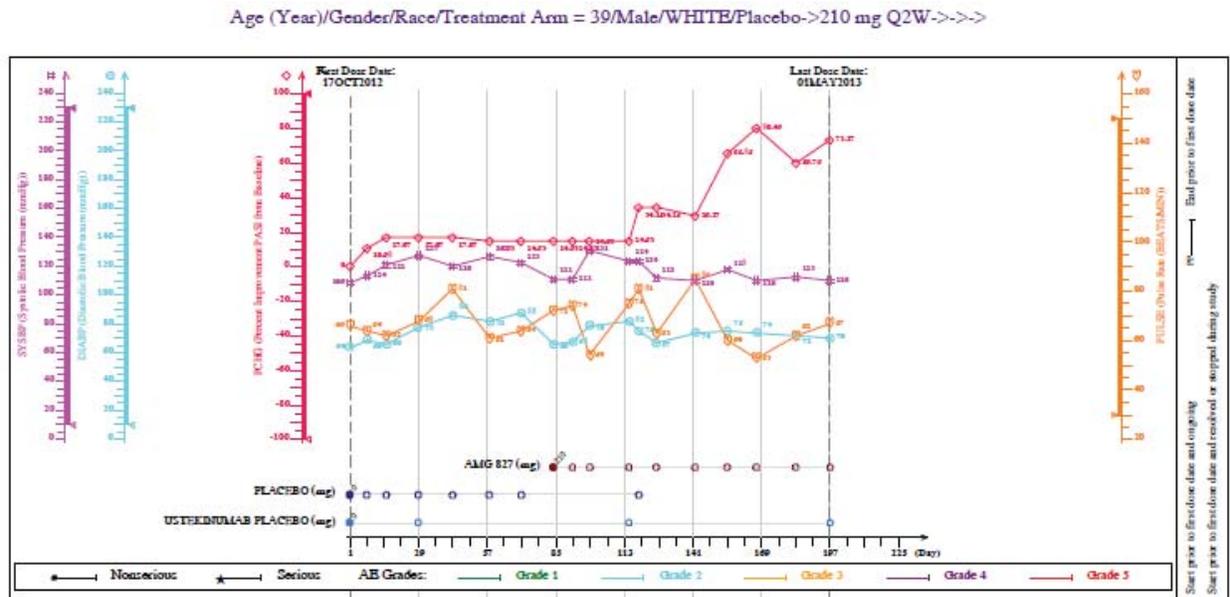
Figure 24: Patient Profile 6003

Study 20120103 Subject 10366026003
 Age (Year)/Gender/Race/Treatment Arm = 54/Male/WHITE/AMG827 210 mg Q2W->210 mg Q2W->210 mg Q2W->



This subject received the CSSRS and PHQ-8 during the maintenance phase of study 103. The subject experienced a significant improvement in psoriasis symptoms with brodalumab 210 mg dosing Q2W for an extended period. He had several negative screening with the implemented CSSRS and PHQ-8, and then completed suicide by jumping off the roof of his apartment building.

Figure 25: Patient Profile 6017



This subject was a 39 year-old male with previous use of adalimumab prior to screening. He was randomized to placebo for 12-week induction and then to brodalumab 210 mg. He completed suicide 140 days into treatment with last dose on (b) (6). No prior medical or psychiatric history was recorded.

The Division also sought an evaluation from our Agency epidemiologists. Two reviews of the safety signal SIB were conducted by the Division of Pharmacovigilance (DPV) and the Division of Epidemiology – I (DEPI-I).

**DPV Review—Robert Levin, MD
 Psoriasis and Psychiatric Morbidity**

Psychiatric and psychological factors play an important role in at least 30% of dermatological disorders.⁹ Patients with psoriasis have a particularly high rate of psychiatric morbidity, including depression, anxiety, suicidal ideation and suicidal behavior, substance use disorders, and other psychiatric disorders. Furthermore, the prevalence of mood symptoms in psoriasis is higher than that observed in many other disfiguring skin disorders.¹⁰ Various authors estimate that the background rate of psychiatric disorders in the psoriasis population ranges from 30% to 45%. One study that performed formal psychiatric assessments in psoriasis patients

⁹ Gupta MA, Gupta AK. Psychiatric and Psychological Co-Morbidity in Patients with Dermatologic Disorders, Epidemiology and Management. Am J Clin Dermatol. 2003;4(12): 833-842

¹⁰ Connor CJ et al. Exploring the Physiological Link between Psoriasis and Mood Disorders. Dermatology Research and Practice.2015;2015: 409637

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demonstrated that 45% of patients met criteria for at least one psychiatric disorder based on diagnostic criteria from the Diagnostic and Statistical Manual of Mental Disorders.¹¹ In this study, the rates of specific psychiatric disorders were as follows: Dysthymia (29%), Major Depression (15%), Alcohol Use disorders (7%), and Generalized Anxiety Disorder (5%). All of these disorders constitute risk factors for suicide. In this study population, 13% had current suicidality. In the literature, the reported rate of suicidal ideation and behavior in psoriasis patients ranges from 7% to 21%, based on a wide variety of assessment types. One large U.K. cohort study of psoriasis patients using the General Practice Research Database (GPRD) estimated that the hazard ratios for depression, anxiety, and suicidal ideation and behavior were 1.39, 1.31, and 1.44, respectively, compared with a control group.¹²

While all of these studies and assessments have various strengths, limitations, and methodological concerns, substantial literature documents that psoriasis patients have an extremely high background rate of psychiatric illness, psychological distress, and substantially impaired quality of life¹. Authors note that the severity of these symptoms and impairment correlates with patients' reported impact of the dermatologic condition on their quality of life related to disfigurement, social anxiety, body image, and self-esteem, rather than objective measures of disease severity. In addition, biological aspects of psoriasis may contribute to mood disorders and other psychiatric disorders associated with psoriasis; these include chronic inflammation, as well as alterations in the hypothalamic-pituitary-adrenal axis and sympathetic nervous system.¹³

Neuropsychiatric Adverse Events in the Psoriasis Studies

We analyzed all neuropsychiatric adverse event data from the 12-week, placebo-controlled phases of the brodalumab psoriasis studies, as well as the maintenance and long-term, open-label phases of the studies. The placebo-controlled and ustekinumab-controlled phases included Phase 3 Trials 02, 03, and 04 and Phase 2 Trial 62. 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. Thus, it is possible that such disorders were under-reported or unrecognized.

In the controlled phases, few psychiatric adverse events were reported, as illustrated in the table below.

¹¹ Singh SM et al. Psychiatric Morbidity in Patients with Psoriasis. *Cutis*. 2016; Feb;97(2): 107-12

¹² Kurd et al. The Risk of Depression, Anxiety, and Suicidality in Patients with Psoriasis: a population-based cohort study. *Arch Dermatol*. 2010 Aug;146(8): 891-5.

¹³ Connor CJ et al. Exploring the Physiological Link between Psoriasis and Mood Disorders. *Dermatology Research and Practice*. 2015;2015: 409637

Table 26: Reported Psychiatric Event in the Placebo-controlled Phases of Brodalumab Studies

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

Source: DPV reviewer analysis of submitted data

Drugs that cause central nervous system or psychiatric adverse reactions tend to be associated with a wide spectrum of neurological, cognitive, psychiatric, and behavioral adverse reactions, rather than a single type of CNS adverse event such as suicidality. In addition, such agents are typically associated with a cluster of such reactions within individuals. For example, drugs associated with an increased risk of suicidality (antidepressants and antiepileptics) also increase the risk of a variety of neurological, cognitive, and psychiatric symptoms. There are other examples of agents associated with a spectrum of CNS reactions. Such a pattern was not evident in the brodalumab studies. There were no apparent significant differences between treatment groups, and there was no clear indication that these were drug-related adverse reactions in the controlled or uncontrolled studies. Furthermore, very few subjects had more than one neuropsychiatric event. However, the data from the controlled phases largely derived from spontaneous reports rather than from prospective, focused assessments of psychiatric symptoms including suicidality; thus, such events were likely to have been under-reported.

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Although there were prospective suicidality assessments during most of the open-label extension studies, there were no prospective assessments of other psychiatric symptoms.

Generally, the majorities of neuropsychiatric adverse events reported in the brodalumab studies were isolated, mild or moderate, transient, and did not result in psychiatric treatment or discontinuation. Furthermore, the vast majority of such events occurred in subjects with a current or past history of psychiatric disorders and treatment. These conditions included depression, anxiety, bipolar disorder, schizophrenia, and substance use disorders. However, there were events that led to psychiatric treatment or discontinuation from the studies, and there were some relevant events reported in individuals without an apparent psychiatric history. Most of the events in the extension phases were captured by the eC-SSRS suicidality queries. Two neurological adverse events (headache and paresthesia) appeared to be drug-related in the controlled phases. Headache was more common in the brodalumab group compared to the placebo and ustekinumab groups (26%, 17%, and 18%, respectively). Paresthesia was more common in the brodalumab and ustekinumab groups than in the placebo group (2.9%, 2.9%, and 0.5%, respectively).

Prospective Assessments of Depression and Anxiety Symptoms in Controlled Phase

One of the controlled Phase 3 psoriasis trials, Study 02, included a systematic, prospective assessment of depression and anxiety symptoms. 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 13 below, subjects in the brodalumab group had higher degrees of improvement in depression and anxiety symptoms compared to the placebo group.

Table 27: Change in HADS Score-Study 20120102 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

Completed Suicides

There were six completed suicides in the brodalumab clinical study programs: four in the psoriasis studies, one in a rheumatoid arthritis study, and one in a psoriatic arthritis study. The available case information was relatively limited; thus, it is extremely difficult to reach conclusions about whether the suicides were related to treatment with brodalumab. All subjects who completed suicide were treated with brodalumab in the long-term, open-label phases of treatment. Two of the patients had a history of psychiatric disorder and treatment or substance use disorder, and four did not have an apparent psychiatric history. Five of these subjects were males between the ages of 39 and 58 years (39, 56, 56, 57, and 58); one was a 36 year-old female. Five of these subjects appeared to have significant financial or psychosocial stressors; some of these appeared to be major stressors. Several subjects completed suicide at least 14 days after their last dose of brodalumab (19, 27, and 58 days after the last dose). One case was possibly not a suicide; the adjudicators concluded that it was indeterminate whether

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the subject intended suicide; the death was possibly secondary to an unintentional heroin overdose.

The completed suicide cases are summarized below:

1. This subject was a 58-year-old Caucasian male from Poland, who participated in a psoriasis trial. He also had a diagnosis of psoriatic arthritis. The subject completed suicide by hanging, 329 days after beginning treatment with brodalumab, and 58 days after his last dose of brodalumab. The subject had no known psychiatric history. On several occasions, he had stated to the investigator that he had ongoing financial distress and debts. There were no reported warning signs before the suicide.
2. This subject was a 56-year-old Asian American male participating in a psoriasis study. This case was adjudicated to be indeterminate regarding suicidal intent. The medical examiner concluded that the case was a suicide, but the investigator and the subject's wife concluded that this was an unintentional heroin and alcohol overdose. The subject had a history of depression and anxiety treated with citalopram and alprazolam, and he appeared to have a history of alcohol use disorder; however, the information was unclear regarding the alcohol use history. He was found dead in his vehicle 97 days after his first dose of brodalumab and 14 days after the last dose. Toxicology results indicated that the subject had ingested heroin; alcohol, alprazolam, and citalopram were also present.
3. This subject was a 39-year-old Caucasian male from the US who participated in a psoriasis study. The subject's mother reported the suicide; the method of suicide is unknown. The subject completed suicide 140 days after first dose of brodalumab and 27 days after the last dose. He had no known psychiatric history. On the last study visit, the subject disclosed to the investigator that he had considerable legal problems and would likely be incarcerated soon. The subject had no other psychiatric adverse events during the study.
4. This subject was a 56-year-old Caucasian male from the US who participated in a psoriasis study. He completed suicide by jumping from the roof of his apartment building 845 days after his first dose of brodalumab and 19 days after the last dose. He had reported that he recently moved to a new apartment and felt stressed and isolated. He had a history of depression and anxiety, and he was treated with trazodone. During the study, the subject reported one brief episode of mild depression. Of note, this subject was screened with the PHQ-8 and eC-SSRS with negative results prior to completing suicide.
5. This subject was a 57-year-old Caucasian male from the US who participated in an open-label study for psoriatic arthritis. He completed suicide with a gun after 2 years and 7 months of brodalumab treatment. The subject had no known psychiatric history. During

the study, he reported a brief episode of decreased energy. Retrospectively, the investigator obtained information about the subject's marital difficulties and complicated social situation.

6. This subject was a 36-year-old Caucasian female enrolled in a US rheumatoid arthritis study. The subject had no apparent psychiatric history. She completed suicide by hanging 4 months after starting treatment with brodalumab. The subject had reported to the investigator that she had been experiencing considerable emotional distress related to reproductive and financial issues. The family reported that there were no warning signs that the subject was planning suicide or had depressive or other symptoms.

DPV Conclusions and Recommendations

We have uncertainty about whether the signal for completed suicide is a risk related to brodalumab treatment. From the available data, we cannot conclude whether or not suicide is a drug-related risk. These populations have a highly elevated risk of psychiatric disorders and symptoms, including SIB. The controlled data do not suggest that neuropsychiatric adverse events are drug-related; however, the controlled phases were relatively short, and there was limited ability to ascertain relevant events. On the other hand, depression and anxiety symptoms improved in a subset of the study population treated with brodalumab who had significant depression or anxiety symptoms at baseline. 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.

DPV Recommendations:

1. Consider approving the brodalumab application for the treatment of psoriasis and clearly describe in labeling the potential risk of suicide, the relevant study results, and emphasize that this is not currently an established drug-related risk.
2. Consider approving brodalumab only as second-line treatment, for patients with an inadequate response to other biologic treatments for psoriasis.
3. Because suicide is a potential risk related to treatment with brodalumab, we could consider potential risk mitigation strategies (Please see review section by Division of Risk Management for a discussion of risk mitigations strategies). DPV postulates the use of a prospective, directed assessment of suicidal ideation and suicidal behavior (e.g., the Columbia-Suicide Severity Rating Scale) during treatment with brodalumab could possibly partially mitigate the risk of SIB including completed suicide. One could assess patients for the presence of SIB at a specific point in time, to assess their current level of

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risk, which could inform management of such patients. However, the use of such an assessment would probably not prevent all suicides; some patients can acutely develop SIB even after a recent negative screen, and there can be false negative assessments, depending on factors related to the patient or rater. Regardless as to whether SIB are related to brodalumab use, such an assessment tool would not be fully effective or reliable in preventing SIB including completed suicide.

4. Would not recommend excluding patients with a history of psychiatric disorders from brodalumab treatment, because it has not been established that there is a drug-related risk of SIB related to brodalumab, and a high proportion of patients with psoriasis have psychiatric disorders.

Reviewer's comment: *A clear relationship could not be established with neuropsychiatric overtones that usually accompany suicidality. It is not clear that this suicidal signal is due to impulsivity with drug related effects. Ascertainment of impulse behaviors and neuropsychiatric adverse events that lead to completed suicides in this any drug program may be difficult to accomplish.*

DEPI Review—Andrew Mosholder, MD

The Division of Epidemiology I (DEPI-I) was asked to compare the 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. However, limitations to this approach should be noted. First, use of external or historical comparisons is not optimal, though it may be necessary when internal controls are insufficient, as was the case here because the data were too sparse. Data from different development programs may be subject to heterogeneity in patient characteristics, follow-up methods, and ascertainment of suicidal adverse events. Only crude pooling of data across trials and products was possible given the availability of data and time constraints, rather than a patient or trial level meta-analysis. Also, safety data specific to psoriasis subjects was not available for all products.

Results of the DEPI-I analysis are shown in the table. Amgen's consultants, Exponent, Inc., prepared a systematic review of psoriasis biologics trials, using publicly available sources; their results are shown in the last row of the table, and were consistent with the DEPI-I review. The suicide rate in brodalumab trials was 3-4 times higher than in trials of other biologics for psoriasis.¹⁴ 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%, per the Exponent, Inc. systematic review of biologics for psoriasis, including psoriasis with psoriatic arthritis). As a thought experiment, if we consider the suicide rate from Exponent's systematic review of Phase 3/4 biologic psoriasis trials the expected rate, brodalumab was associated with

¹⁴ For some products, clinical trial data for other indications were included, as shown in the table of individual products that follows.

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a 3-fold higher than expected suicide rate (58 suicides/100,000 patient years vs 19 suicides/100,000 patient years), equivalent to roughly one excess suicide per every 2600 person-years of use.

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Table 28: Comparative 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).

Details of the clinical trial rates of SIB with individual psoriasis products are shown in the table below.

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Table 29: Rates of Suicide across all Psoriasis biologics

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

The DEPI-I review concluded:

1. Meaningful comparisons of brodalumab SIB rates to placebo or active controls are not available from the brodalumab development program, because of the short duration of exposure to those comparators, and the relative infrequency of SIB events.
2. Comparisons to development programs for other psoriasis products, biologics and one small molecule, indicate an inordinate number of completed suicides in brodalumab clinical trials.
3. The incidence of suicidal behavior and ideation appears to have been underestimated prior to use of the eCSSRS. Rates per 100 person-years of suicidal ideation and any suicidal behavior prior to eCSSRS monitoring were 0.06 and 0.11, and with eCSSRS monitoring were 0.59 and 0.20, respectively.
4. Subjects with a past psychiatric history for depression or SIB had a much higher rate of SIB. In the sponsor's analysis, patients with, versus without, a past history of depression had rates of SIB per 100 person-years of 1.40 and 0.21, respectively; for patients with versus without a past history of suicidality, the rates were 2.30 and 0.12. However only 2 of the 6 subjects who committed suicide had a positive psychiatric history.
5. Though the eCSSRS improved ascertainment of SIB, the data are not adequate to determine whether the eCSSRS reduced the rate of attempted or completed suicide. Two subjects committed suicide shortly after a negative eCSSRS.
6. There does not appear to be a good rationale for separating data on SIB in psoriasis trials from SIB data in other indications.
7. 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.

Existing pharmacovigilance and pharmacoepidemiology methods will not be adequate to assess the risk of SIB with brodalumab in the post-marketing environment. FAERS data would be difficult to interpret because of under-reporting of SIB events, and the expected baseline rate of events given the comorbidity of depression with psoriasis. A pharmacoepidemiology study would also be difficult; a recent systematic review highlighted the challenges of studying suicide and suicide attempts in health care claims data settings.¹⁵

DEPI-I Recommendations: Although a causal relationship of SIB to brodalumab use is uncertain, to the extent there is currently "insufficient information about the drug to determine whether the product is safe for use," a Complete Response per 21 CFR 314.125(b)(4) could be considered.

As noted above, in brodalumab trials, subjects with a past psychiatric history for depression or

¹⁵ . Walkup JT, Townsend L, Crystal S. and Olfson M. A systematic review of validated methods for identifying suicide or suicidal ideation using administrative or claims data. *Pharmacoepidemiol Drug Saf*, 2012; 21(S1): 174–182

SIB had substantially higher rates of SIB. Accordingly, if brodalumab is approved, restricting its use to patients without a relevant past psychiatric history would reduce the number of SIB events among brodalumab users, regardless of the extent to which those SIB events are causally related; screening by a mental health professional at baseline could be considered. Judging from the experience in the brodalumab clinical trials, clinical monitoring of users with the eCSSRS would greatly improve the chances of detecting SIB, so that patients could be directed to obtain treatment and discontinue brodalumab. A Risk Evaluation and Mitigation Strategy (REMS) could be considered to help implement these practices. Labeling and a Medication Guide, as proposed by the sponsor, would help communicate this issue to prescribers and patients. Finally, no post marketing observational data collection would be recommended at this time, given the limitations of such data for suicidal outcomes.

Table 30: Rates of Suicide Behavior across IL17 Products

	N	Exposed PY	Completed suicides N	Suicide Behaviors/Attempts N	Suicides+Attempts/ 100,000 PY	Ideation/ 100,000PY	Adjudicated w/ C-CASA?
Brodalumab All trials	6243	10438	6	18	229.9	229.9	No
Ixekizumab	4209	6480	0	9	140	0	Yes
Secukinumab PsO, PsA	3928	3225	0	1	31	31	Yes

Source: Adapted from Agency DEPI-I review

Reviewer’s comment: *The data does not conclusively reveal a direct relationship between SIB and brodalumab; however, the rates of completed suicides are convincing on its own. This reviewer acknowledges the limitations to definitive conclusions regarding the safety signal across trial and products. The conclusions and recommendation of DPV and DEPI will be considered for final regulatory decision.*

Psychiatry Consult Review—Jean Kim, MD

DDDP had requested consultation with Division of Psychiatry Products (DPP) in March 2014 to seek advice regarding psychiatric adverse events in Phase 3 trials after several reports of suicidal ideation or behavior (SIB) were reported to the Agency. The consultative review was completed by Cara Alfaro, Pharm.D., in July 2014 and recommended safety changes such as administration of the Columbia Suicide Severity Rating Scale (C-SSRS), cutoff scores for the Patient Health Questionnaire-8 (PHQ-8) or Beck Depression Inventory (BDI) for both study entry and for safety monitoring during the study, additional exclusion criteria to screen out severe SIB cases, and a quantitative analysis of the comparative SIB signal between treatment and control groups. The sponsor agreed to add the C-SSRS to monitor for SIB (which changed some of the exclusion criteria mid-study, in May 2014); the recommendations were communicated to them in meetings before DPP’s review was finalized. There was also a blinded, independent

adjudication of all potential SIB events identified from a list of MedDRA terms, with subsequent classification using the Columbia-Classification Algorithm for Suicide Assessment (C-CASA).

The DPP was consulted again by DDDP to review the data from the BLA submission, and to provide input on safety concerns about psychiatric adverse effects associated with brodalumab, such as suicidal ideation and behavior, and to clarify whether these events are a primary drug effect or reflect the background occurrence of these events in a patient population that has higher rates of depression and suicidal ideation and behavior.

The review is primarily of the three global pivotal, Phase 3 placebo-controlled clinical trials (02, 3, and 04).

These trials all began with a 12-week placebo-controlled induction phase that will be the focus of this review. Subsequent to that phase of each study, patients were re-randomized to drug, placebo, or active control, rendering cross-treatment comparisons unreliable primarily because of loss of the randomized character of the treatment groups beyond the initial 12 weeks.

Table 31 enumerates the number of patients in the safety samples for the induction phase in each of the three trials.

Table 31: Enumeration of Patients in the Induction Phase of the Phase 3 Trials

Study	Placebo	Brodalumab 140mg q2wks	Brodalumab 210mg q2wks	Ustekinumab
2012-0102	220	219	222	0
2012-0103	309	607	612	300
2012-0104	313	626	622	313
TOTAL	842	1452	1456	613

Discontinuation rates during the induction phase for each treatment group for all three studies were low (less than 6% in Study 2012-0102 and less than 5% in the other two trials).

Subjects with moderate to severe psoriasis, who had known comorbid psychiatric conditions such as depression, substance abuse, or prior suicidal behavior, were NOT initially excluded from the Phase 3 brodalumab trials. Basically, there were no psychiatric exclusion criteria in the Phase 3 initial study protocols. Some assessment of past psychiatric history (reported by subject or presence of psychiatric medication) was done at baseline screening visit as part of routine medical history, and if present was recorded in subjects' baseline medical history.

After concerns were raised in a February 2014 sponsor letter about a possible SIB signal, and after subsequent FDA discussion and recommendations, the electronic C-SSRS¹⁶ and PHQ-8¹⁷

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were added via protocol amendment in May 2014 to monitor subjects for suicidality and depression respectively. (See specific criteria below.) Subjects in the studies who were subsequently flagged by the revised screening scales were discontinued and referred to mental health professionals.

The eCSSRS and PHQ-8 were used to monitor psychiatric safety in their subjects starting in May 2014 (midway through these trials). These ratings were not performed during the induction phases of the three Phase 3 trials.

In addition to the tools described above, the Hospital Anxiety and Depression Scale (HADS) a 14-item scale, to which the patient responds with a self-rating of 0-3 on 7 symptoms of depression and 7 symptoms of anxiety, was included to monitor subjects' psychiatric symptoms during one study's induction phase: it was collected at baseline and Week 12 in Study 20120102 only and in a small number of subjects.

After implementation of the eC-SSRS and PHQ-8, all subjects were re-consented to inform them of the potential risk of SIB and required to take these self-rated scales. Neither was implemented during the 12-week induction phase for any Phase 3 trials since that phase ended for all subjects by late 2013. The adverse events during that period were retroactively identified and adjudicated for classification via the Columbia Classification Algorithm of Suicide Assessment (C-CASA), as discussed in Sections D and E.

Any positive score on the CSSRS (any report of SIB) triggered discontinuation from the study and a mental health referral. Any PHQ-8 score 10 or greater triggered mental health referral and 15 or greater triggered study discontinuation.

Primary analysis was to occur at week 12 and at withdrawal endpoints up until week 52 (which went on up until August 2014 for some subjects). Interim analyses were planned (to include the CSSRS and PHQ-8) after 80% of subjects reached week 132 in the study, and after all subjects completed week 266, as well as annual safety analyses until the study was closed.

After May 22, 2015, all the brodalumab clinical trials were stopped by Amgen and subjects did not continue to take the study drug past late June 2015. AstraZeneca subsequently took over

¹⁶ The eCSSRS is a standardized and validated instrument developed for the assessment of the severity and frequency of suicidal ideation and behavior (Mundt et al, 2010; Posner et al, 2011). Subjects respond to standardized clinical questions that are presented in a uniform fashion. The eCSSRS defines five subtypes of suicidal ideation and of behavior in addition to self-injurious behavior with no suicidal intent. The eCSSRS takes approximately 3 to 10 minutes to complete.

¹⁷ The PHQ-8 is a validated and widely used eight-item version of the Patient Health Questionnaire depression scale designed to clinically assess patients for symptoms and signs of depression (Kroenke and Spitzer, 2002; Kroenke et al, 2009). The PHQ-8 takes approximately 3 minutes to complete.

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the drug's development, and they have continued follow-up safety analyses and scale screening. The 4-Month Safety Update was submitted in March 2016 with data through November 2015.

SIB Event Identification

The safety dataset included SIB 33 events in 28 different subjects. The difference from my findings is explained by 2 subjects with events classified by the sponsor as non-treatment-emergent events and thus excluded from their ADSIB dataset. In both cases, it is not clear to me that the exclusion of these patients was justified. Thus, I have included them in rate calculations.

Incidence of Induction Phase SIB Events

During the initial 12-week induction period only, my review noted 2 subjects with SIB events: 1 subject on brodalumab and 1 subject on ustekinumab. No one on placebo had any SIB events during that 12-week period. Incidence rates are not adjusted for exposure because dropout rates for both treatment groups during the induction phases were very low.

Table 32: 12-Week Induction Phase Suicidal Events/Subjects

	Subjects	Events
Brodalumab	1	2
Ustekinumab	1*	2*
Placebo	0	0

*excluded by sponsor as non-treatment related, but included here

Table 33: Incidence based on the 12-week Induction Phase

	Event Subjects/Total Subjects	Percentage
Brodalumab	1/2908	0.03%
Ustekinumab	1/613	0.16%
Placebo	0/842	0.00%

Using a 2-tailed Fisher's exact test, the differences between the SIB rates for brodalumab versus placebo and brodalumab versus ustekinumab were not statistically significant at an alpha level of 0.05 (p-values of 0.22 and 0.32, respectively).

Incidence of Post-Induction Phase SIB Events

For the rest of the 52-week study period and extension phases, it is difficult to infer drug causality to SIB events because of the re-randomization that occurred at the start of this phase, which resulted in loss of the original randomized properties of the treatment groups. Therefore, I did not compute incidence or perform a comparative analysis of SIB rates.

There were 9 events that occurred during the rest of the 52-week period (1 was by the same individual who had 2 events in the induction phase of trial 03). Three of these events were on ustekinumab and 6 were on brodalumab.

Table 34: Week 13 to Week 52 Suicidal Events/Subjects

	Subjects	Events
Brodalumab	6 *	6 *
Ustekinumab	3	3
Placebo	n/a	n/a

*1 subject same as subject in Induction Phase

There were 21 more events by 18 subjects that occurred during an open-label follow-up extension phase during which all subjects received brodalumab (there was no placebo or active control arm). This phase was intended to continue for 5 years total but ended May 22, 2015. (There was 1 additional event by trial 03 that the sponsor considered non-treatment-related. I will include this subject here.) This includes the data through March 2015.

Table 35: Follow-Up Extension Phase (2013-2014 through March 2015)

	Subjects	Events
Brodalumab	18*	21*

*1 subject excluded by sponsor but included here

There were 4 completed suicides overall, 2 occurring during the 52-week study (not during the induction period) and 2 during the open-label extension phase. All had been treated with brodalumab. (There have reportedly been 2 other suicides in the other brodalumab trials for psoriatic/rheumatoid arthritis.)

In addition, there was a 4-Month Safety Update Report sent by the sponsor in March 2016 which covered new adverse events for several months after the last ADAE dataset cut off in late March 2015. The safety data cutoff for this update was November 2015. Upon review, this set included 7 new SIB events all occurring April to July 2015 among subjects in post-induction phase of the Phase 3 trials (There was also 1 new SIB event from someone in another open-

label study). 4 had suicidal ideation and 4 had suicide attempts; none were completed suicides, all had been actively exposed to brodalumab during the extension phase. (One had not taken brodalumab since 3 months prior though.)

The CSSRS and PHQ-8 were routinely implemented midway through the Brodalumab study program as per FDA recommendation in late May 2014. To identify SIB events that occurred prior to this, the sponsor retroactively conducted a search of relevant MedDRA terms which were adjudicated for classification according to the C-CASA with a cutoff date of November 2014.

The implementation of these monitoring tools seems to have identified more SIB events during the latter part of the trials and during the long-term extension period than were detected earlier in the trials. Per the sponsor, the reported rate of suicidal behavior almost doubled and the reported rate of suicidal ideation increased 10-fold after subjects began completing the eCSSRS. The rate of completed suicides decreased slightly after implementation of the eCSSRS.

Table 36: Suicidal adverse events in brodalumab psoriasis trials before and after eCSSRS implementation (from sponsor)

Event	Pre eC-SSRS N=4464 Pyr 5383.3		Post eC-SSRS N=3823 Pyr 2530.2	
	n	Rate/100 pyrs	n	Rate/100 pyrs
Completed suicide	3	0.06	1	0.04
Any suicidal behavior	6	0.11	5	0.20
Suicidal ideation	3	0.06	15	0.59

Source: DEPI review

So the exposure-adjusted rates of suicidal ideation and attempts were greater after implementation compared to the pre-CSSRS period. However, these were not concurrent, randomized groups. There was confounding by time, so an alternative explanation to enhanced ascertainment is that the risk of events is higher with a longer duration of exposure. Also, there may be other uncontrolled factors at play due to lack of randomization.

The PHQ-8 detected more frequent mild score elevation in brodalumab versus ustekinumab, although one cannot extrapolate conclusions due to scale usage after the placebo-controlled induction phase.

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For the HADS used in Study 02 only during the induction phase, the results showed improved scores in brodalumab versus placebo, but only a small number of the study subjects completed the scale; given the small number of subjects, the results are not reliable.

Conclusions and Recommendations

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

One might also consider a possible beneficial effect on depression and anxiety based on the HADS finding in one placebo-controlled study 2012-0102, where the brodalumab arm showed significant improvement in levels of depression/anxiety symptoms detected by the HADS versus placebo. Again though, the findings are limited by relatively small sample size and possible confounding (situational reaction to improved skin symptoms, etc.)

I have ongoing concerns about the lack of ability to make any definitive conclusions about the relationship between brodalumab and suicidality based on the existing data, and the adequacy of currently available pharmacovigilance methods to detect events during the post marketing period, and whether any proposed REMS recommendations would be helpful in preventing suicides if the risk factors for SIB remain uncertain.

Given all this uncertainty, I recommend that the sponsor conduct an active-controlled, parallel group study with brodalumab focusing on frequent monitoring for psychiatric symptoms, especially suicidal ideation and behavior but also depressive symptoms. The active control agent should be a psoriasis agent which appears to have low risk for SIB events. This may permit better understanding of the relationship between brodalumab treatment and SIB as well as determination of risk factors for SIB, which might inform a future REMS. It is further recommended that this study be conducted prior to approval, because of the current availability of safe and effective agents to treat psoriasis and the potential for fatal and other serious sequelae of suicidal behavior that might be produced by brodalumab treatment if a true causal relationship exists. This will likely have to be a large study of considerable length. DPP is willing to work with FDA dermatology experts, epidemiologists, and statisticians in designing such a trial.

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As per general DPP recommendations, SIB events during clinical trials are best assessed prospectively using a validated instrument like the CSSRS. The ongoing usage of such scales is highly recommended to detect systematically ongoing SIB events during future studies.

Reviewer's comment: This reviewer agrees with our DPP colleagues. 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.

8.5.2. Major Cardiovascular Adverse 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.

The theoretical mechanism of action is antibodies affecting cytokine levels that are thought to have an effect on the inflammatory processes of cardiovascular disorders.¹⁸ Brodalumab, an IL17A receptor antagonist, block the effects of IL17 at the receptor site, resulting in a compensatory increase in circulating IL17¹⁹; the increase in IL17A then impacts other cytokines in the cascade.²⁰ The theoretical effect is accelerating cardiovascular outcomes.

Evidence suggested that ustekinumab may have a positive risk for MACE; however, in the controlled trials with ustekinumab, there were no association found with MACE events. The Agency conducted an epidemiological study examining the associations of ustekinumab and MACE, and found no associations to cardiovascular adverse events.²¹ Of note, briakinumab use

¹⁸ SU, Sheng-an. MA, Hong. Shen, Li. Interleukin-17 and Acute Coronary Syndrome. Journal of Zhejiang University – Science B (*Biomed & Biotechnol*): 2013 14(8): 664-669.

¹⁹ See Clinical Pharmacology section on IL17 affecting IL6

²⁰ Wang, Jie. Brodalumab treatment increased serum IL-17A concentrations in Study 20120102. Agency Clinical Pharmacology Review of Applicant Submission BLA 761032.

²¹ MacCloskey, C. Review of Janssen's Report on "Analysis of MACE, Other Thrombotic Events and Other

(monoclonal IgG antibody directed at IL-12/23) was associated with an increased risk of MACE in one of four Phase 3 trials. The applicant withdrew its product applications pending before the FDA and the European Medicines Agency (EMA) prior to completion of their reviews.²²

This analysis used the 120-day safety update dataset. Because the study was not designed, and consequently not powered, to compare the treatment arms with respect to MACE, we did not conduct statistical testing.

Table 37: Baseline Characteristics of the Safety Population in Phase 3 Psoriasis Trials

n (%)	Brodalumab n = 2908	Placebo n = 842	Ustekinumab n = 613
Male	2021 (69)	586 (70)	417 (68)
Age (years)			
Mean (SD)	44.9 (12.9)	44.7 (12.9)	45.1 (13.1)
< 40	1049 (36)	325 (39)	220 (36)
45-64	1672 (57)	464 (55)	351 (57)
> = 65	187 (6)	53 (6)	42 (7)
BMI (> 35 kg/m ²)	636 (22)	167 (20)	135 (22)
Biologic usage	874 (30)	266 (32)	160 (26)
History of psoriasis arthritis	616 (21)	174 (21)	114 (19)
History of ischemic heart disease	101 (3)	31 (4)	24 (4)
History of cardiac or vascular disorders	926 (32)	248 (29)	212 (35)

Source: DB7 analysis of submitted data

The table above summarizes subject baseline characteristics by original treatment arms.

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).

Cardiovascular Events in Ustekinumab Clinical Studies, PSOLAR and Postmarketing Data,” August 25, 2014. FDA/OSE/OPE: 20-MAR-2015.

²² Traczewski P and L Rudnicka. Briakinumab for the treatment of plaque psoriasis. *Biodrugs* 2012; 26(1):9 -20.

Table 38: Number (%) and follow-up time-adjusted Incidence Rates of adjudicated MACE in the active-controlled Phase (52 weeks) of the three Phase 3 Psoriasis Trials

MACE	Brodalumab n = 3711	Bro after Ustek n = 124	Ustekinumab n = 489	Placebo n = 39
Number (%)				
MACE	22† (0.6)	0	1 (0.2)	0
CV death	1 (0.0)	0	0	0
MI	16 (0.5)	0	1 (0.2)	0
Stroke	5 (0.13)	0	0	0
Follow-up time	3297.2	75.5	494.8	
Incidence rate*	0.7	0	0.2	0
MACE	Brodalumab + Brodalumab after Ustekinumab n = 3835			
Number (%; 95% CI)	22 (0.6, 0.38–0.90)			
Follow-up time	3372.7			
Incidence rate* (95% CI)	0.7 (0.43–1.02)			

Source: DB7 analysis of submitted data

†One subject (20120103-10366037013) was originally in the placebo arm and was excluded from this analysis because MACE occurred before the first dose of brodalumab.

*per 100 subject-years

From randomization to end of follow up, 48 MACE events occurred among brodalumab users, where 1 MACE event occurred in a subject who switched to brodalumab after receiving ustekinumab. The incidence of MACE among subjects exposed to brodalumab was 1.1% (95% CI: 0.83–1.49) and the follow-up adjusted incidence rate was 0.6 per 100 subject-years (95% CI: 0.42–0.76).

Table 39: Number (%) and follow-up time-adjusted adjudicated MACE incidence rates in Psoriasis Trials from Day 1 to the end-of-follow-up

MACE	Brodalumab n = 3706	Bro after Ustek n = 567	Ustekinumab n = 49	Placebo n = 41
Number (%)				
MACE	47† (1.3)	1* (0.2)	2 (4.1)	0
CV death	8 (0.2)	0	1 (2.0)	0
MI	28 (0.8)	0	1 (2.0)	0
Stroke	11 (0.3)	1 (0.2)	0	0
Follow-up time	7587.1	778.1	27.5	
Incidence rate**	0.7	0.3	7.3	0
MACE	Brodalumab + Brodalumab after Ustekinumab			
	n = 4273			
Number (%; 95% CI)	48 (1.1, 0.83–1.49)			
Follow-up time	8365.2			
Incidence rate** (95% CI)	0.6 (95% CI: 0.42–0.76)			

†Six MACE were excluded from brodalumab only arm because 1) 4 events occurred >42 days after the last dose of brodalumab; 2) one CV death (20120103-10366037013) occurred before the first dose of brodalumab and the subject was originally assigned in the placebo arm; and 3) one CV death (20120102-10248019002) was re-adjudicated as non-MACE

*One CV death was excluded from brodalumab after ustekinumab arm because it occurred >42 days after the last dose of brodalumab

**per 100 subject years

The Table below summarizes the follow-up time-adjusted incidence rates of MACE by reported age and medical history in psoriasis trials from randomization to end of the follow-up. As expected, the incidence rate of MACE was higher in brodalumab users over 65 years old compared to those younger. Brodalumab users with a history of ischemic heart disease had a 9-fold increase in incidence rate of MACE compared to users without history. Similarly, brodalumab users with a history of cardiac or vascular disorder had a 4.7 fold increase in incidence rate compared to users without history.

Table 40: Number (%) and follow-up time-adjusted incidence of MACE by age and Medical History in Psoriasis Trials from Randomization to end-of-follow-up

Subgroups	No. of brodalumab users (subject-years) N = 4464	No. of MACE (%)	Incidence rate per 100 subject-years
Age (years)			
< 40	1559 (3070)	5 (0)	0.16
40 - 64	2439 (4765)	33 (1)	0.69
>= 65	275 (530)	10 (4)	1.89
Ratio of >= 65/< 40			11.8
History of ischemic cerebrovascular conditions or ischemic heart disease			
Yes	152 (265)	11 (7)	4.15
No	4121 (8101)	37 (1)	0.46
Ratio of Yes/No			9.02
History of cardiac or vascular disorders			
Yes	1356 (2541)	32 (2)	1.26
No	2917 (5824)	16 (1)	0.27
Ratio of Yes/No			4.67

Source: DB7 analysis of submitted data

Consultation Summary

Division of Epidemiology-I (Dr. Andrew Mosholder)

The Division of Epidemiology-I was asked to provide assistance in comparing the rate of MACE in trials of brodalumab versus other products indicated for psoriasis. It has been proposed that IL-17 has a pathogenic role not only in psoriasis but also in atherosclerosis, and that this may be one explanation for the fact that psoriasis is a risk factor for cardiovascular disease. As brodalumab treatment was found to raise serum IL-17A concentrations in the clinical development program, this could possibly mean that brodalumab treatment might accelerate atherosclerosis and increase MACE. With respect to cardiovascular safety issues with other biologics for psoriasis, the tumor necrosis factor (TNF) blockers etanercept, adalimumab, and infliximab are labeled for an association with heart failure, though not MACE. However, there have been previous concerns about MACE with the anti-IL-12/23 agents ustekinumab and briakinumab (of which only ustekinumab is marketed).

We examined the brodalumab trial data on MACE. In the 12-week placebo controlled trial periods, and 52-week ustekinumab controlled trial periods, MACE outcomes were very sparse in the comparison groups (see DB7 summary review, above), so comparisons of MACE rates between brodalumab and controls are not informative. Accordingly, clinical trial data from

recent regulatory submissions for other psoriasis products were surveyed for data on MACE to provide comparisons to brodalumab (Table).

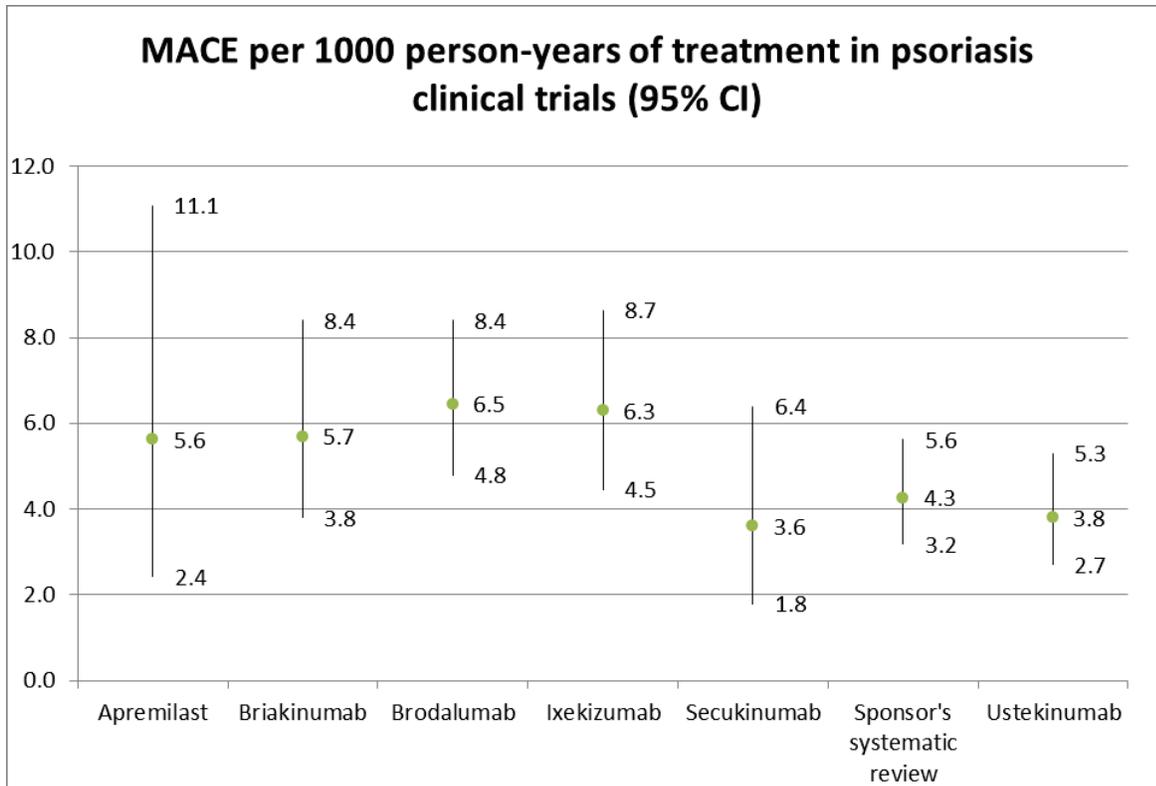
Table 41: Rates of major adverse cardiovascular events (MACE) with treatment by specific products in psoriasis clinical trials

Psoriasis product	N	Exposure pyr	MACE	CV death	MI	Stroke	MACE per 1000 pyr	CV death per 1000 pyr	MI per 100 pyr	Stroke per 1000 pyr	MACE outcomes adjudicated (y/n)?
Brodalumab, Psoriasis Phase 3 trials only (with 4 mo su)	4,273	8365.2	54	12	30	12	6.46	1.43	3.59	1.43	y
Apremilast (1)	1,184	1,422	8	n/a	n/a	n/a	5.63	n/a	n/a	n/a	y
Briakinumab (2)	2,520	4,704	27	5	19	3	5.74	1.06	4.04	0.64	y
Ixekizumab (3)	4,035	6,026.4	38	7	25	6	6.31	1.16	4.15	1.00	y
Secukinumab (4)	3,494	n/a	11*	1	5	6	3.6	0.3	1.6	2.0	n
Ustekinumab (5)	3,705	9,442	36	2	30	4	3.81	0.21	3.18	0.42	y

Summary data across products are subject to heterogeneity in patient characteristics, follow-up methods, & ascertainment of events. Data sources: (1) 4 mo su; (2) Langley et al. JEADV 2013, 27, 1252–1261; (3) 4 mo su; (4) MACE Information Request response; (5) MACE Information Request response
 *Categories not mutually exclusive
 pyr=patient-years, 4 mo su=4 month safety update
 An analysis of MACE for adalimumab, etanercept, or infliximab could not be located

Numerically, brodalumab had the highest rate of MACE across products, and also the numerically highest rate of CV death. The following graph displays the incidence rates and 95% confidence intervals for MACE in psoriasis clinical trials for the indicated products; it can be seen that while the brodalumab rate was highest, MACE rates were fairly similar for brodalumab, apremilast, briakinumab and ixekizumab.

Figure 26: MACE per 1000 person-years of treatment in Psoriasis Clinical Trials



Source: DEPI reviewer's compilation

There are important limitations to these data. First, use of external or historical comparisons is generally not as valid as internal controls. Data from different development programs may be subject to heterogeneity in patient characteristics, follow-up methods, and ascertainment of MACE. The results reflect only a crude pooling of data across trials and products, rather than a patient or trial level meta-analysis, and do not take into account potential differences in confounders across programs.

Further evaluation of the risk of MACE with brodalumab is recommended, given the plausible association of MACE with elevated serum IL-17 levels resulting from brodalumab treatment. A cardiovascular outcome randomized clinical trial would be challenging, but would provide the highest quality data. If brodalumab is approved, there are reliable observational techniques for studying MACE which could be applied post-marketing—but only if the market uptake of brodalumab is sufficient to provide a large enough sample. Analysis of the existing clinical trial data on IL-17 levels among brodalumab-treated subjects could provide insights into the possible association with MACE, if it were to be found that subjects with greater IL-17 increases had higher rates of MACE events.

Division of Cardio-Renal Products (Dr. Senatore Fortunato)

IL-17A levels have been associated with psoriasis and cardiovascular disease based on similar pathophysiology, but its role in various stages of atherosclerosis and its complications remains poorly understood. Although IL-17A serum levels are elevated consequent to brodalumab therapy, an enhanced potential for IL-17A mediated acute coronary syndrome might be theoretically offset by a protective effect from brodalumab in blocking receptors that might propagate IL-17A mediated MACE.

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. There was also wide variation of median time from last dose to MACE (-74 days to + 24 days) thus raising doubt about drug causality. The follow-up-time adjusted adjudicated MACE incidence rates per 100 subject-years from Day 1 to end of follow-up (\pm 2 years) was low (0.6%) in the brodalumab arms compared to that of ustekinumab (7.3%). The elevated rate in the ustekinumab arm was likely due to an artifact associated with a low sample size in that arm (n=49) compared to brodalumab (n= 3706 + 567 = 4273) following therapeutic switches to brodalumab. Subjects with a medical history of ischemic cerebrovascular conditions or ischemic heart disease were 9 times more likely than subjects without this history to have a MACE while on the trial from Day 1 to the end of follow-up. Similarly, subjects with a history of cardiac or vascular disorders by MedDRA were 4.7 times more likely than subjects without this history to have a MACE in this trial from Day 1 to end of follow-up. This data showed that the higher cardiac risk patients were more likely to have a MACE but did not show a drug-mediated effect.

Conclusion

No specific safety signals for MACE from the phase 3 clinical trials evaluating brodalumab in patients with psoriasis were detected.

Reviewer's Discussion:

The applicant concluded that the evidence does not support a causal relationship between brodalumab and MACE. This reviewer acknowledges the lack of direct evidence to support an association between brodalumab and MACE in the Phase 3 clinical trials with psoriasis patients. However, theoretical evidence from literature provides some mechanistic association of increase IL-17 cytokine and atherosclerosis. A full literature review conducted by the Division of Cardio-Renal Products and Dr. Senatore revealed mixed results and concluded that there is inconclusive

evidence to establish causation. Lack of long-term clinical trial data prevents further analysis of this mechanistic role in cardiovascular and cerebrovascular adverse events. The early termination of clinical trials in subjects with chronic plaque psoriasis and the lack of controlled data to establish no effect are not available. Our epidemiology colleagues used cross trial comparison data, which has limitations, to show that there is higher rate of MACE in brodalumab users compared to other biologic treatments on the market currently.

This reviewer finds that although there is insufficient evidence directly implicating brodalumab and MACE, the lack of data is the primary issue. Proper labeling can remediate some risk. Cardiovascular risk factors should be reviewed prior to selecting brodalumab as treatment in psoriasis patients. Section 5, Warnings and Precautions will need to describe the cardiovascular safety issues. A post marketing study directed at collecting cardiovascular adverse events should be requested.

8.6. Safety Analyses by Demographic Subgroups

Tables 42 and 43 present the PGA 0 or 1 success 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.

Table 42: Success on the sPGA⁽¹⁾ at Week 12 by Baseline Demographics for Trials 02 and 03

	Trial 02			Trial 03			
	Brodalumab 210 mg N=222	Brodalumab 140 mg N=219	Placebo N=220	Brodalumab 210 mg N=612	Brodalumab 140 mg N=610	Placebo N=309	Ustekinu- mab N=300
Gender							
<i>Female</i>	48/61 (79%)	27/57 (47%)	1/59 (2%)	151/191 (79%)	122/197 (62%)	6/90 (7%)	63/95 (66%)
<i>Male</i>	120/161 (75%)	91/162 (56%)	2/161 (1%)	330/421 (78%)	232/413 (56%)	6/219 (3%)	120/205 (59%)
Age							
<65	154/206 (75%)	106/199 (53%)	3/202 (1%)	458/585 (78%)	332/572 (58%)	11/289 (4%)	174/279 (62%)
≥65	14/16 (88%)	12/20 (60%)	0/18 (0%)	23/27 (85%)	22/38 (58%)	1/20 (5%)	9/21 (43%)
Race							
<i>White</i>	152/203 (75%)	103/196 (53%)	2/202 (1%)	435/551 (79%)	323/557 (58%)	9/273 (3%)	166/271 (61%)
<i>Non-white</i>	16/19 (84%)	15/23 (65%)	1/18 (6%)	46/61 (75%)	31/53 (58%)	3/36 (8%)	17/29 (59%)
Weight							
≤100 kg	133/156 (85%)	99/156 (63%)	3/159 (2%)	358/428 (84%)	297/426 (70%)	11/216 (5%)	135/214 (63%)
>100 kg	35/66 (53%)	19/63 (30%)	0/61 (0%)	123/184 (67%)	57/184 (31%)	1/93 (1%)	48/86 (56%)
Prior Biologic Use							
<i>Yes</i>	85/105 (81%)	47/99 (47%)	0/101 (0%)	133/177 (75%)	90/179 (50%)	1/90 (1%)	42/84 (50%)
<i>No</i>	83/117 (71%)	71/120 (59%)	3/119 (3%)	348/435 (80%)	264/431 (61%)	11/219 (5%)	141/216 (65%)
Region							
<i>U.S.A.</i>	60/87 (69%)	41/86 (48%)	3/88 (3%)	209/286 (73%)	138/281 (49%)	5/144 (3%)	79/140 (56%)
<i>Canada</i>	40/48 (83%)	23/49 (47%)	0/47 (0%)	53/64 (83%)	37/66 (56%)	2/33 (6%)	23/32 (72%)
<i>Ex-North America</i>	68/87 (78%)	54/84 (64%)	0/85 (0%)	219/262 (84%)	179/263 (68%)	5/132 (4%)	81/128 (63%)

Source: Reviewer Table. (1) sPGA score of 0 or 1.

Table 43: Success on the sPGA⁽¹⁾ at Week 12 by Baseline Demographics for Trial 04

	Trial 03			
	Brodalumab 210 mg N=624	Brodalumab 140 mg N =629	Placebo N=315	Ustekinumab N=313
Gender				
<i>Female</i>	146/193 (76%)	121/192 (63%)	5/107 (5%)	62/101 (61%)
<i>Male</i>	351/431 (81%)	256/437 (58%)	8/208 (4%)	117/212 (55%)
Age				
<65	467/578 (81%)	354/589 (60%)	11/300 (4%)	168/292 (58%)
≥65	30/46 (65%)	23/40 (58%)	2/15 (13%)	11/21 (52%)
Race				
<i>Caucasian</i>	448/565 (79%)	345/569 (61%)	13/294 (4%)	162/280 (58%)
<i>Non-white</i>	49/59 (83%)	32/60 (53%)	0/21 (0%)	17/33 (52%)
Weight				
≤100 kg	386/458 (84%)	319/462 (69%)	11/233 (5%)	132/227 (58%)
>100 kg	111/166 (67%)	58/167 (35%)	2/82 (2%)	47/86 (55%)
Prior Biologic Therapy				
<i>Yes</i>	114/157 (73%)	83/160 (52%)	3/76 (4%)	39/75 (52%)
<i>No</i>	383/467 (82%)	294/469 (63%)	10/239 (4%)	140/238 (59%)
Region				
<i>U.S.A.</i>	203/276 (74%)	160/278 (58%)	7/141 (5%)	78/140 (56%)
<i>Canada</i>	59/72 (82%)	40/75 (53%)	0/34 (0%)	23/38 (61%)
<i>Ex-North America</i>	235/276 (85%)	177/276 (64%)	6/140 (4%)	78/135 (58%)

Source: Reviewer Table. (1) sPGA score of 0 or 1.

Efficacy by Country

Trials 02 was conducted in 6 countries that included the US, Canada, France, Germany, Poland, and Switzerland. Trial 03 was conducted in 10 countries that included the US, Australia, Austria, Canada, Czech Republic, France, Hungary, Netherlands, Poland and Spain. Trial 04 was conducted in 11 countries that included the US, Australia, Belgium, Canada, France, Greece, Hungary, Italy, Latvia, Poland, and Russia. In all three Phase 3 trials, the country that enrolled the most subjects was the US with 261 subjects (39%), 851 subjects (46%) and 835 subjects (44%) in Trials 02, 03, and 04, respectively.

Tables 44, 45, and 46 present the results for the co-primary endpoints at Week 12 by country for Trials 02, 03, and 04, respectively. 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.

Table 44: Success on the sPGA⁽¹⁾ and PASI 75 Response at Week 12 by Country (Trial 02)

	Country	Brodalumab 210 mg	Brodalumab 140 mg	Placebo
sPGA 0 or 1	USA	60/87 (69%)	41/86 (48%)	3/88 (3%)
	Canada	40/48 (83%)	23/49 (47%)	0/47 (0%)
	France	11/14 (79%)	7/10 (70%)	0/12 (0%)
	Germany	15/21 (71%)	12/20 (60%)	0/20 (0%)
	Poland	36/45 (80%)	29/45 (64%)	0/45 (0%)
	Switzerland	6/7 (86%)	6/9 (67%)	0/8 (0%)
PASI 75	USA	68/87 (78%)	51/86 (59%)	5/88 (6%)
	Canada	42/48 (88%)	27/49 (55%)	0/47 (0%)
	France	12/14 (86%)	7/10 (70%)	1/12 (8%)
	Germany	17/21 (81%)	13/20 (65%)	0/20 (0%)
	Poland	40/45 (89%)	29/45 (64%)	0/45 (0%)
	Switzerland	6/7 (86%)	5/9 (56%)	0/8 (0%)

Source: Reviewer's table. (1) sPGA score of 0 or 1.

Table 45: Success on the sPGA⁽¹⁾ and PASI 75 Response at Week 12 by Country (Trial 03)

	Country	Brodalumab 210 mg	Brodalumab 140 mg	Placebo	Ustekinumab
sPGA 0 or 1	USA	235/286 (82%)	166/281 (59%)	13/144 (9%)	92/140 (66%)
	Australia	37/40 (93%)	26/39 (67%)	1/19 (5%)	16/20 (80%)
	Austria	6/6 (100%)	4/8 (50%)	0/4 (0%)	1/2 (50%)
	Canada	56/64 (88%)	47/66 (71%)	3/33 (9%)	25/32 (78%)
	Czech Republic	17/18 (94%)	16/20 (80%)	1/8 (13%)	6/7 (86%)
	France	11/14 (79%)	10/13 (77%)	3/8 (38%)	5/9 (56%)
	Hungary	18/18 (100%)	11/15 (73%)	1/10 (10%)	7/8 (88%)
	Netherlands	5/5 (100%)	5/6 (83%)	0/3 (0%)	3/3 (100%)
	Poland	116/130 (89%)	100/132 (76%)	0/64 (0%)	45/65 (69%)
	Spain	16/19 (84%)	14/20 (70%)	1/10 (10%)	7/10 (70%)
PASI 75	USA	235/286 (82%)	166/281 (59%)	13/144 (9%)	92/140 (66%)
	Australia	37/40 (93%)	26/39 (67%)	1/19 (5%)	16/20 (80%)
	Austria	6/6 (100%)	4/8 (50%)	0/4 (0%)	1/2 (50%)
	Canada	56/64 (88%)	47/66 (71%)	3/33 (9%)	25/32 (78%)
	Czech Republic	17/18 (94%)	16/20 (80%)	1/8 (13%)	6/7 (86%)
	France	11/14 (79%)	10/13 (77%)	3/8 (38%)	5/9 (56%)
	Hungary	18/18 (100%)	11/15 (73%)	1/10 (10%)	7/8 (88%)
	Netherlands	5/5 (100%)	5/6 (83%)	0/3 (0%)	3/3 (100%)
	Poland	116/130 (89%)	100/132 (76%)	0/64 (0%)	45/65 (69%)
	Spain	16/19 (84%)	14/20 (70%)	1/10 (10%)	7/10 (70%)

Source: Reviewer table. (1) sPGA score of 0 or 1.

Table 46: Success on the sPGA⁽¹⁾ and PASI 75 Response at Week 12 by Country (Trial 04)

	Country	Brodalumab 210 mg	Brodalumab 140 mg	Placebo	Ustekinumab
sPGA 0 or 1	USA	203/276 (74%)	160/278 (58%)	7/141(5%)	78/140(56%)
	Australia	15/17 (88%)	7/16 (44%)	0/8 (0%)	2/9(22%)
	Belgium	7/8 (88%)	4/8 (50%)	0/6 (0%)	1/2 (50%)
	Canada	59/72 (82%)	40/75 (53%)	0/34 (0%)	23/38 (61%)
	France	26/28 (93%)	21/29 (72%)	2/16 (13%)	10/15 (67%)
	Greece	17/21 (81%)	11/23 (48%)	0/10 (0%)	5/11 (45%)
	Hungary	16/17 (94%)	10/16 (63%)	0/7 (0%)	8/10 (80%)
	Italy	2/2 (100%)	2/3 (67%)	0/2/(0%)	1/1 (100%)
	Latvia	28/33 (85%)	19/32 (59%)	0/16 (0%)	9/15 (60%)
	Poland	106/127 (83%)	89/129 (70%)	4/63 (6%)	40/63 (63%)
	Russia	18/23 (78%)	14/21 (67%)	0/12 (0%)	2/9 (22%)
PASI 75	USA	224/276 (81%)	188/278 (68%)	10/141(7%)	92/140(66%)
	Australia	16/17 (94%)	10/16 (63%)	0/8 (0%)	6/9 (67%)
	Belgium	7/8 (88%)	4/8 (50%)	0/6 (0%)	1/2 (50%)
	Canada	64/72 (89%)	44/75 (59%)	1/34 (3%)	23/38 (61%)
	France	26/28 (93%)	21/29 (72%)	1/16 (6%)	12/15 (80%)
	Greece	18/21 (86%)	15/23 (65%)	0/10 (0%)	8/11 (73%)
	Hungary	16/17 (94%)	12/16 (75%)	0/7 (0%)	9/10 (90%)
	Italy	2/2 (100%)	2/3 (67%)	0/2/(0%)	1/1 (100%)
	Latvia	30/33 (91%)	23/32 (72%)	1/16 (6%)	13/15 (87%)
	Poland	113/127 (89%)	98/129 (77%)	4/63 (6%)	48/63 (76%)
	Russia	15/23 (65%)	15/21 (71%)	2/12 (17%)	4/9 (44%)

Source: Reviewer table. (1) sPGA score of 0 or 1.

Efficacy by Disease Severity

In all three trials, the treatment effect was generally lower for subjects with a baseline sPGA score of 4 (severe) or 5 (very severe) compared to those subjects with baseline sPGA score of 3 (moderate). It should be noted that there was only a small number of subjects with sPGA score of 5. **Table 47** presents the results for the sPGA response at Week 12 by baseline disease severity for Trials 02, 03, and 04.

Table 47: Success on the sPGA⁽¹⁾ at Week 12 by Baseline sPGA severity

	Baseline sPGA	Brodalumab 210 mg	Brodalumab 140 mg	Placebo	Ustekinumab
Trial 02	3	99/121 (82%)	79/129 (61%)	3/114 (3%)	N/A
	4	58/87 (67%)	33/80 (41%)	0/91 (0%)	
	5	11/14 (79%)	6/10 (60%)	0/15 (0%)	
Trial 03	3	257/316 (81%)	236/358 (66%)	7/167 (4%)	99/153 (65%)
	4	198/254 (78%)	105/217 (48%)	5/120 (4%)	73/132 (55%)
	5	26/42 (62%)	13/35 (37%)	0/22 (0%)	11/15 (73%)
Trial 04	3	306/373 (82%)	274/412 (67%)	9/192 (5%)	120/192(63%)
	4	175/226 (77%)	94/192 (49%)	4/113 (4%)	51/103 (50%)
	5	16/25 (25%)	9/25 (36%)	0/10 (0%)	8/18 (44%)

Source: Reviewer's Table; (1) sPGA score of 0 or 1

Reviewer's comment: *The subgroup analysis did not reveal any specific treatment enhancement for any special groups.*

8.7. Specific Safety Studies/Clinical Trials

Studies in immunogenicity and cytokine interaction are discussed in the Clinical Pharmacology sections of this review. No other specific safety studies were conducted by the applicant.

8.8. Additional Safety Explorations

8.8.1. Human Carcinogenicity or Tumor Development

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 sponsor submitted literature reports to assess 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. There is evidence that Th17 cells and/or IL-17A/IL-17RA may be involved in both pro- and anti-tumorigenic processes, although the majority of data seems to point towards the protumorigenic role. Th17 cells and IL-17A have been implicated in promoting tumor growth in xenografts and syngeneic tumors in mice via promotion of angiogenesis and down-regulation of anti-tumor immunity. With the absence or reduction of IL-17A (using IL-17A^{-/-} mice or treatment with anti-IL-17A antibodies), tumor growth was reduced.

This suggests that inhibition of IL-17 signaling by blocking IL-17RA by administration of brodalumab may result in an anti-tumorigenic environment. Other studies have shown that IL-17A and/or Th17 cells can reduce tumor growth by stimulating anti-tumor immunity and reducing angiogenic stimuli. These studies were generally conducted by introducing exogenous IL-17A, either by transfection of tumor cells with IL-17A expression vectors or by adoptive transfer of tumor targeted-Th17 cells, mechanisms which may be less likely to be relevant for the potential impact of brodalumab (which would be reducing IL-17A signaling). From the data already available, it is evident that the impact of blocking IL-17 signaling is likely to be highly dependent on the situation and context. The net effect may depend on the type of tumor, the stage of tumorigenesis, the tumor location, and the immune system status and function, among other variables.

Reviewer's comment: Post marketing surveillance of malignancy report frequency compared to background rates may provide the most accurate determination of cancer risk for brodalumab. The suggestion of a registry to follow the malignancy rates in patients receiving biologics is acceptable.

8.8.2. Human Reproduction and Pregnancy

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

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2 to 4% and 15 to 20%, respectively.

There are no data on the presence of brodalumab in human milk, the effects on the breastfed infant, or the effects on milk production.

8.8.3. Pediatrics and Assessment of Effects on Growth

The safety and efficacy of brodalumab have not been evaluated in pediatric patients.

8.8.4. Overdose, Drug Abuse Potential, Withdrawal, and Rebound

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This is a monoclonal antibody drug product; no abuse potential is seen with this product.

8.9. Safety in the Postmarket Setting

8.9.1. Safety Concerns Identified Through Postmarket Experience

Not applicable.

8.9.2. Expectations on Safety in the Postmarket Setting

Based on the Agency recommendations, a restrictive program with post-marketing study(s) will be required for this drug product. Specifically, a randomized controlled trial with active controls will be required to further evaluate risk, should the drug product be approved. A registry for patients will also be required to further evaluate risk to MACE and infections for patients on drug.

8.10. Additional Safety Issues From Other Disciplines

None

8.11. Integrated Assessment of Safety

Overall, the safety profile for brodalumab has not been fully explored. A signal for suicide ideations and behavior exists with an unusually high number of completed suicides in all-brodalumab clinical programs. This safety signal need to be further quantified in this population that is already vulnerable for psychiatric adverse events.

9 Advisory Committee Meeting and Other External Consultations

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, Building 31 Conference Center, the Great Room (Rm. 1503), 10903 New Hampshire Avenue, Silver Spring, Maryland. The committee discussed biologics license application (BLA) 761032, brodalumab injection, a human monoclonal antibody, submitted by Valeant Pharmaceuticals Luxembourg S.a.r.l., proposed for the treatment of moderate to severe plaque psoriasis in adult patients who are candidates for systemic therapy or phototherapy.

Attendance:

Dermatologic and Ophthalmic Drugs Advisory Committee Members Present (Voting): Michael Bigby, MD (Chairperson); Ken Katz, MD, MSc, MCSE

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Dermatologic and Ophthalmic Drugs Advisory Committee Members Not Present (Voting):

Richard M. Awdeh, MD (Chairperson); Geoffrey G. Emerson, MD, PhD; Mary E. Maloney, MD; Stephen S. Feman, MD, MPH, FACS; Mildred M.G. Olivier, MD; David K. Yoo, MD

Dermatologic and Ophthalmic Drugs Advisory Committee Member Present (Non-Voting):

Marla B. Sultan, MD, MBA (Industry Representative)

Temporary Members (Voting): Bonnie H. Arkus, RN (*Acting Consumer Representative*); Warren B. Bilker, PhD; Michael J. Blaha, MD, MPH; Erica Brittain, PhD; John J. DiGiovanna, MD; Lynn A. Drake, MD; Michael R. Irwin, MD; Francis E. Lotrich, MD, PhD; Stephen R. Marder, MD; Elaine H. Morrato, DrPH, MPH; Matthew V. Rudorfer, MD; **Elizabeth Smith (*Patient Representative*)**; **Ming T. Tan, PhD**; Consuelo Walss-Bass, PhD; David D. Waters, MD; **Julie M. Zito, PhD**

FDA Participants (Non-Voting): Amy Egan, MD, Kendall A. Marcus, MD; Gary Chiang, MD, MPH; Cynthia L. LaCivita, PharmD; Simone P. Pinheiro, ScD, MSc

Designated Federal Officer (Non-Voting): Jennifer Shepherd, RPh

Open Public Hearing Speaker: Tena Brown

Questions to the Committee:

1. **DISCUSSION:** Discuss the safety data for brodalumab.

A. **DISCUSSION:** Do the safety data for brodalumab suggest a signal for:

- i. Suicide Ideation and Behavior (SIB)?
- ii. Major Adverse Cardiovascular Events (MACE)?

B. **DISCUSSION:** If you believe there is a safety signal for SIB and/or MACE, comment on possible approaches to further evaluate these signals.

Committee Discussion: *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. Please see the transcript for details of the committee discussion.

2. **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. Please see the transcript for details of the committee discussion.*

3. **DISCUSSION:** If you voted for approval in question #2, please comment on post-marketing studies/trials that are needed to further define the safety of brodalumab, including, but not limited to, the need for long-term studies to evaluate suicidality and cardiovascular events.

Committee Discussion: *Several committee members stated their concerns that a mandatory registry could be a barrier to drug access for some patients, but supported a voluntary registry. One committee member expressed concern that the endpoints information*

collected by the sponsor may not be rigorous enough. Another committee member stated that patients on brodalumab may need additional clinician support, such as from a social worker or a psychologist. Please see the transcript for details of the committee discussion.

The meeting was adjourned at approximately 4:00 p.m.

10 Labeling Recommendations

10.1. Prescribing Information

Labeling recommendations are contained in the reviewer's comments. Labeling negotiations are still ongoing. If approval is recommended, a BOX WARNING and WARNING AND PRECAUTIONS sections of the label will be required to contain all the relevant safety issues for this product. In addition, limitations of use sections will be added and contraindications will contain an SIB recommendation.

10.2. Patient Labeling

A Medication Guide has been submitted by the applicant. REMS discussion is ongoing within the Agency.

10.3. Nonprescription Labeling

Not applicable.

11 Risk Evaluation and Mitigation Strategies (REMS)

This reviewer is recommending a pre-approval randomized control trial that extends into the post-approval period. This RCT should be conducted in a similar fashion as the pivotal clinical trials with active control arm(s). The concept of this single clinical trial should be conducted for evaluation of safety and does not have to be powered for efficacy. The pre-approval period should be a 52-week treatment period with brodalumab and active control arm(s) with full assessment of neuropsychiatric adverse events and prospective review of CSSRS and PHQ-8. In addition to the full ascertainment of depression and depressive symptoms, this trial should evaluate Hospital Anxiety Depression Scales (HADS) and CASA as the data for 52-week becomes available. This clinical trial does not need to be fully powered for detection of complete suicide or suicide attempts. The trial can be conducted with similar power to the pivotal clinical trials.

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On completion of the 52-week periods, the data will be analyzed in totality with the available clinical data to provide the benefit/risk evaluation for approval.

If brodalumab is recommended for approval, I would still push for this clinical trial in the post-approval period as part of a PMR. I believe this is the most effective way to evaluate the SIB risk.

The Agency met with the applicant in a teleconference on 22-AUG-2016 to discuss our recommendations regarding labeling and REMS for approval of brodalumab. The meeting minutes are provided in summary:

Meeting Purpose: We would like to discuss the following: Boxed Warning and proposed REMS. We are continuing to discuss internally what, if any, post marketing requirements will be necessary.

- Subsequent to the July 19th Advisory Committee meeting, FDA has conducted internal meetings regarding options for the potential approval of the brodalumab application. These discussions have included senior management from CDER, OND, and OSE.
- While acknowledging the seriousness of the disease (moderate to severe psoriasis), the availability of alternative treatments with comparable efficacy profiles, and the presence of a potentially fatal risk (SIB) observed in the clinical development program for brodalumab, we have determined that, if this product is to be approved, it will require a REMS with ETASU in addition to optimized labeling, to mitigate the risk of suicidality observed with your product.

A. Optimized labeling would include:

1. A **Boxed Warning** discussing the potential increased risk of suicidality with brodalumab
2. A **Limitation of Use** that brodalumab should only be used in patients who have failed to respond, or lost response, to other biologic therapies
3. A **recommendation to discontinue therapy** or reassess need in patients who do not achieve an adequate response within 12 weeks

B. The REMS with ETASU should include: Prescriber Certification, Pharmacy Certification, and Documentation of Safe Use conditions. The REMS appended materials should include:

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

We will be reviewing the elements to be included and referencing specific examples from other approved REMS Programs. Although we are providing examples of REMS materials, they are for the purpose of layout and format. Some content may not be applicable to your proposed REMS and should be revised to reflect only the elements and requirements we have discussed today.

1. **Prescriber certification**: Ensures that prescribers are educated on the potential risk of suicidal ideation and behavior (SIB) observed with brodalumab therapy, acknowledge understanding of the risk, and agree to counsel patients about this risk
 - Prescriber Certification should include: A 1- or 2-page document titled “**SILIQ REMS Program Healthcare Provider Enrollment Form**”
 - Refer to the “Addyi REMS Program Prescriber Enrollment Form” for reference:
http://www.accessdata.fda.gov/drugsatfda_docs/rems/Addyi_2016-05-10_Prescriber_Enrollment_Form.pdf
 - However, at this time, a Prescriber and Pharmacy Training Program (as referenced in the “Addyi REMS Program Prescriber Enrollment Form”) are not necessary.
 - Formatting of the “SILIQ REMS Program Healthcare Provider Enrollment Form” should include:
 - Instructions for stakeholders at the top of the document, as seen in the Lemtrada REMS Prescriber Enrollment Form:
http://www.accessdata.fda.gov/drugsatfda_docs/rems/Lemtrada_2016-04-05_Prescriber_Enrollment_Form.pdf

- Check boxes next to each attestation in order to ensure each attestation is reviewed
 - For an example of check boxes, see the Entereg REMS Program Hospital Pharmacy Enrollment Form:
http://www.accessdata.fda.gov/drugsatfda_docs/regs/Entereg_2016-06-01_Pharmacy_Enrollment_Form.pdf
 - Healthcare Provider contact information at the end of the form, as seen with the “Addyi REMS Program Prescriber Enrollment Form”:
http://www.accessdata.fda.gov/drugsatfda_docs/regs/Addyi_2016-05-10_Prescriber_Enrollment_Form.pdf
- Healthcare Provider Certification should also include a “Patient Wallet Card”
 - We have reviewed your proposed Patient Wallet Card and request that you include the following elements:
 - Indication
 - Acknowledgement of risk seen with brodalumab therapy (regardless of whether or not patient has history of SIB)
 - Warning signs of suicide
 - Referral to the National Suicide Prevention Lifeline
 - It is the Agency’s preference that this information be included on wallet-size cardstock, similar to the Soliris REMS Patient Safety Card:
http://www.accessdata.fda.gov/drugsatfda_docs/regs/Soliris_2016-07-12_Patient_Safety_Card.pdf), Zinbryta REMS Patient Wallet Card:
http://www.accessdata.fda.gov/drugsatfda_docs/regs/Zinbryta_2016-05-27_Patient_Wallet_Card.pdf), or the iPledge REMS Patient ID Card (see p. 82 of the iPledge REMS Educational Kit for Female Patients Who Can Get

Pregnant):

http://www.accessdata.fda.gov/drugsatfda_docs/rems/Iso_tretinoin_2016-07-08_Educational_Kit_For_Female_Patients_Who_Can_Get_Pregnant.pdf

2. **Pharmacy certification**: Ensures that brodalumab prescribers are certified and patients are enrolled in the SILIQ REMS Program.
 - Pharmacy certification should include a 1-2 page document titled **“SILIQ REMS Program Pharmacy Enrollment Form”**
 - Refer to the Sabril REMS Program Pharmacy Enrollment Form as an example:
http://www.accessdata.fda.gov/drugsatfda_docs/rems/Sabril_2016-06-27_Pharmacy_Enrollment%20Form.pdf
3. **Documentation of Safe Use Conditions**: Ensures that patients are: counseled by their prescriber on the potential risk of SIB, understand the potential risk associated with brodalumab treatment, and are aware of the need to seek medical attention should they experience an emergence or worsening of suicidal thoughts or behavior
 - Documentation of Safe Use Conditions should include a **“SILIQ REMS Program Patient-Provider Agreement Form”**
 - Refer to the Addyi REMS Program Patient-Provider Agreement Form as an example:
http://www.accessdata.fda.gov/drugsatfda_docs/rems/Addyi_2016-05-10_Patient-Provider_Agreement.pdf
4. **REMS website**: Provides a resource for stakeholders, with the ability to access and print REMS materials
 - Consider a “SILIQ REMS Program Website” similar to: Sabril’s:
<https://www.sabrilrems.com/>

5. Although, we provided examples of REMS materials, they are for the purpose of layout and format. Some content may not be applicable to your proposed REMS and should be revised to reflect only the elements and requirements we have discussed today.
6. We cannot begin working on the REMS until we have a substantially complete agreed upon label. Therefore, efforts should be turned to accomplishing that as quickly as possible.

The applicant stated they would not be able to provide a response to our request as described above in the time frame the Agency recommended. Negotiations continue to proceed with the applicant at this time.

11.1. Safety Issue(s) that Warrant Consideration of a REMS

For the issue of SIB, restrictive REMS will be recommended if the drug is to be approved. Labeling will include a Boxed Warning and limitations on use. The drug will be identified as a second line agent for the use in moderate to severe plaque psoriasis. The REMS will include elements to assure safe use (ETASU) with a prescriber certification and a pharmacy certification as well as conditions for safe use. These requirements are still under negotiation with the applicant.

In addition to the SIB safety issues, the Agency will require patients to participate in a registry. The registry will evaluate further AEs for MACE, SIB, and infections. This registry is still under negotiations with the applicant.

11.2. Conditions of Use to Address Safety Issue(s)

See above for description of REMS.

11.3. Recommendations on REMS

This reviewer is recommending a Complete Response due to lack of safety data to assure safe use of the drug product in this vulnerable population. If the drug is to be approved, The REMS and restricted use a second line therapy is acceptable to this reviewer. Current recommendations on REMS are being discussed in the Agency with DRISK and negotiations on these REMS are being held with the applicant.

12 Postmarketing Requirements and Commitments

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My recommendation would be for a pre-approval Randomized control trial to further ascertain the SIB signal in a multiple active arms. It is my opinion that neuropsychiatric events in non-psychiatric trials are under reported; however, based on the risk margins obtained in the currently submitted Phase 3 clinical trials, our biostatisticians are able to make sample size calculations for a clinical trial based on safety.

Figure 27: Safety Trials on SIB with Brodalumab—Sample Size Calculations

Risk Margin	Total No. of Events	Person-Years by Background Rate			No. of Subjects by Background Rate (Trial duration 1 year)			No. of Subjects by Background Rate (Trial duration 2 years)		
		0.1%	0.2%	0.4%	0.1%	0.2%	0.4%	0.1%	0.2%	0.4%
1.2	1264	1,264,000	632,000	316,000	1,264,000	632,000	316,000	63,200	321,000	158,000
1.5	255	255,000	127,500	63,750	255,000	127,500	63,750	127,500	63,750	31,875
2.0	87	87,000	43,500	21,750	87,000	43,500	21,750	43,500	21,750	10,875
2.5	50	50,000	25,000	12,500	50,000	25,000	12,500	25,000	12,500	6,250

Based on the above calculations, it would be difficult to enroll a trial of these sizes to adequately power the study.

This reviewer would not be recommending a clinical trial that would be impracticable to conduct. A pre-approval RCT or a PMR RCT could be to conduct a trial similar to the three Phase 3 clinical trials submitted for review. Since two of the three clinical trials had completed suicides, a fourth clinical trial can be conducted to evaluate ascertainment of neuropsychiatric adverse events and SIB. This data could be combined to either lend further evidence of drug-SIB relationship or to refute the relationship. An extension of active arms to a full 5-year can evaluate safety for long-term use.

The Agency continues to negotiate a PMR with the applicant that will be sensible and help ascertain the SIB signal.

13 Appendices

13.1. References

1. CDC- National Vital Statistics. Suicide Rates in US (1999-2014).
2. Connor CJ et al. Exploring the Physiological Link between Psoriasis and Mood Disorders. *Dermatology Research and Practice*. 2015;2015: 409637
3. Gananca L, Oquendo MA, Tyrka AR, Cisneros-Trujillo S, Mann JJ, Sublette ME. The role of cytokines in the pathophysiology of suicidal behavior. *Psychoneuroendocrinology*. 2016;63:296-310.
4. Gupta MA, Gupta AK. Psychiatric and Psychological Co-Morbidity in Patients with Dermatologic Disorders, *Epidemiology and Management*. *Am J Clin Dermatol*. 2003;4(12): 833-842
5. Henry W. Lim, MD et al. Phototherapy in dermatology: A call for action. *JAAD*. Vol # 72: 6, June 2015, Pages 1078–1080
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9. Liu Y, Ho RC, Mak A. The role of interleukin (IL)-17 in anxiety and depression of patients with rheumatoid arthritis. *Int J Rheum Dis*. 2012;15(2):183-7.
10. Ma X, Reynolds SL, Baker BJ, Li X, Benveniste EN, Qin H. IL-17 enhancement of the IL-6 signaling cascade in astrocytes. *J Immunol*. 2010;184(9):4898-906.
11. MacCloskey, C. Review of Janssen’s Report on “Analysis of MACE, Other Thrombotic Events and Other Cardiovascular Events in Ustekinumab Clinical Studies, PSOLAR and Postmarketing Data,” August 25, 2014. FDA/OSE/OPE: 20-MAR-2015.
12. Singh SM et al. Psychiatric Morbidity in Patients with Psoriasis. *Cutis*. 2016; Feb;97(2): 107-12

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13. Traczewski P and L Rudnicka. Briakinumab for the treatment of plaque psoriasis. *Biodrugs* 2012; 26(1):9 -20.
14. Walkup JT, Townsend L, Crystal S. and Olsson M. A systematic review of validated methods for identifying suicide or suicidal ideation using administrative or claims data. *Pharmacoepidemiol Drug Saf*, 2012; 21(S1): 174–182

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13.2. Financial Disclosure

In compliance with 21 CFR Part 54, Amgen forwarded a Certification/Disclosure Form to the clinical investigators and sub-investigators who participated in covered clinical studies for brodalumab. Prior to study initiation, the investigators were requested to certify to the absence of certain financial interests or arrangements or to disclose, as required, those financial interests or arrangements as delineated in 21 CFR 54.4(a)(3)(i-iv). In addition, investigators were requested to notify Amgen if there is any change to the information given for up to one year after the study ended. No clinical investigators and/or sub-investigators who participated in the studies are full or part-time employees of Amgen.

Covered Clinical Study (Name and/or Number): 20090062, 20090403, 20120102, 20120103, 20120104

Was a list of clinical investigators provided:	Yes <input checked="" type="checkbox"/>	No <input type="checkbox"/> (Request list from Applicant)
Total number of investigators identified: <u>215</u>		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): <u>0</u>		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): <u>8</u>		
<p>If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)):</p> <p>Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: <u>0</u></p> <p>Significant payments of other sorts: <u>1</u></p> <p>Proprietary interest in the product tested held by investigator: <u>0</u></p> <p>Significant equity interest held by investigator in S</p> <p>Sponsor of covered study: <u>0</u></p>		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes <input checked="" type="checkbox"/>	No <input type="checkbox"/> (Request details from Applicant)
Is a description of the steps taken to	Yes <input checked="" type="checkbox"/>	No <input type="checkbox"/> (Request information

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minimize potential bias provided:		from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) <u>0</u>		
Is an attachment provided with the reason:	Yes	No <input type="checkbox"/> (Request explanation from Applicant)

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

/s/

GARY T CHIANG
08/25/2016

DAVID L KETTL
09/16/2016

See CDTL review which does not recommend a Complete Response.

CLINICAL OUTCOME ASSESSMENT CONSULT REVIEW

CLINICAL OUTCOME ASSESSMENT (COA) TRACKING NUMBER BLA NUMBER	AT 2016-030 761032
LETTER DATE/SUBMISSION NUMBER PDUFA GOAL DATE DATE OF CONSULT REQUEST	November 16, 2015 / SDN 1, eCTD 0000 November 2, 2016 February 12, 2016
REVIEW DIVISION MEDICAL REVIEWER REVIEW DIVISION PM	The Division of Dermatology and Dental Products Gary Chiang Strother Dixon
PRIMARY COA REVIEWER SECONDARY COA REVIEWER ASSOCIATE DIRECTOR, COA STAFF (ACTING)	Yasmin Choudhry Selena Daniels Elektra Papadopoulos
REVIEW COMPLETION DATE	July 12, 2016
ESTABLISHED NAME TRADE NAME SPONSOR	Brodalumab (human monoclonal immunoglobulin G2 (IgG2) 140 and 210 mg subcutaneous injection TBD Valeant Pharmaceuticals Luxembourg S.a.r.l.
CLINICAL OUTCOME ASSESSMENT TYPE	Patient-reported outcome
ENDPOINT(S) CONCEPT(S) MEASURE(S) INDICATION INTENDED POPULATION(S)	Psoriasis symptom/signs severity Psoriasis Symptom Inventory Treatment of moderate-to-severe plaque psoriasis Adult patients with moderate-to-severe plaque psoriasis

Clinical Outcome Assessment Review

Yasmin Choudhry, M.D.

BLA 761032

Brodalumab

Psoriasis Symptom Inventory (Symptom severity)

A. EXECUTIVE SUMMARY

This Clinical Outcome Assessment (COA) review is provided as a response to a request for consultation by the Division of Dermatology and Dental Products (DDDP) regarding BLA 761032 Brodalumab (subcutaneous injection) for the treatment of moderate-to-severe plaque psoriasis.

DDDP requested COA Staff to review the patient-reported outcome (PRO) assessment used in the three phase 3 brodalumab clinical trials to assess the signs and symptoms of psoriasis.

The PRO efficacy assessment used as key secondary endpoint was the Psoriasis Symptom Inventory (PSI; Appendix A). Therefore, the review focused on the adequacy of the PSI to support the applicant's targeted labeling claims (listed in Section 1.4 of this review).

This submission included an evidence dossier describing the development of the PSI. The review concludes that the evidence submitted by the applicant sufficiently demonstrates that PSI is a well-defined and reliable assessment and fit-for-purpose in the context of this particular drug development program to assess the signs and symptoms of psoriasis in pivotal trials. Furthermore, PSI is adequate to support a labeling claim related to improvement in psoriasis signs and symptoms (i.e., itching, redness, scaling, burning, stinging, cracking, flaking, and pain).

B. BACKGROUND INFORMATION

Materials reviewed:

- PRO Evidence Dossier (SDN 1, eCTD #0000) received November 16, 2015 (dated May 12, 2015)
- DDDP Consult dated February 12, 2016 to review the original BLA 761032; Sequence 0000

1 CONTEXT OF USE (COU)

1.1 Target Study Population and Clinical Setting

The target population for the brodalumab clinical trials was adult patients (age ≥ 18 years) with moderate to severe plaque psoriasis, defined as having a body surface area (BSA) $\geq 10\%$, a PASI ≥ 12 , and sPGA ≥ 3 at screening and baseline. The clinical study protocols (20120101, 20120102, and 20120103) outline the inclusion and exclusion criteria.

Clinical Outcome Assessment Review

Yasmin Choudhry, M.D.

BLA 761032

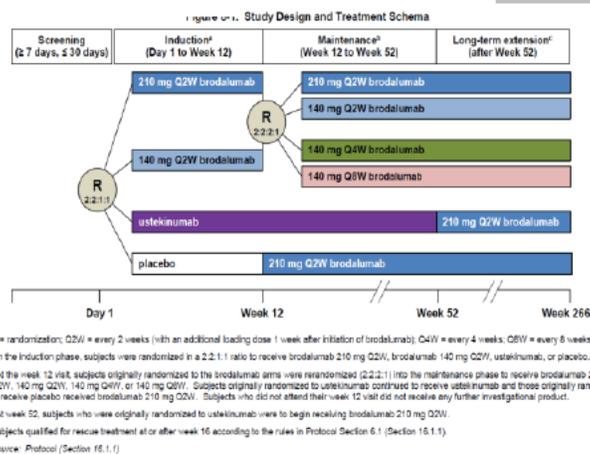
Brodalumab

Psoriasis Symptom Inventory (Symptom severity)

1.2 Clinical Trial Design, Protocol, and Analysis Plan

Three phase 3 brodalumab clinical trials (studies: 20120101, 20120102, and 20120103) were conducted to establish efficacy. The phase 3 studies were randomized, double-blind, and double-dummy studies to evaluate the efficacy and safety of brodalumab compared with placebo and ustekinumab in subjects with moderate to severe plaque psoriasis. Below is an illustration of the overall study design:

APPEARS THIS WAY ON ORIGINAL



The clinical review provides further details of the study designs.

1.3 Endpoint Positioning

The endpoint model is as follows:

Endpoint Model and Hierarchy for Clinical Trials for the Treatment of Moderate to Severe Plaque Psoriasis

Efficacy Endpoint	Concept	Measure
Primary/ co-primary	Severity of plaque psoriasis	sPGA 0 or 1 at week 12 (vs. placebo)
	Area of involvement and severity of plaque psoriasis	PASI 75 at week 12 (vs. placebo) PASI 100 at week 12 (vs. ustekinumab)
Key secondary	Severity of plaque psoriasis	sPGA 0 at week 12
	Area of involvement and severity of plaque psoriasis	PASI 100 at week 12
	Severity of plaque psoriasis signs and symptoms	PSI at week 12

PASI = Psoriasis Area Severity Index,
 PSI = Psoriasis Symptom Inventory,
 sPGA = static Physician Global Assessment

A responder analysis was used as the endpoint for PSI. The pre-specified responder definition was: *A PSI total score of ≤ 8 with no item score > 1 .*

Clinical Outcome Assessment Review

Yasmin Choudhry, M.D.

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Psoriasis Symptom Inventory (Symptom severity)

Reviewer comment: The Dermatology Life Quality Index (DLQI) was another PRO assessment, but was not specified in the statistical hierarchy as a key secondary endpoint and is not further discussed in this review.

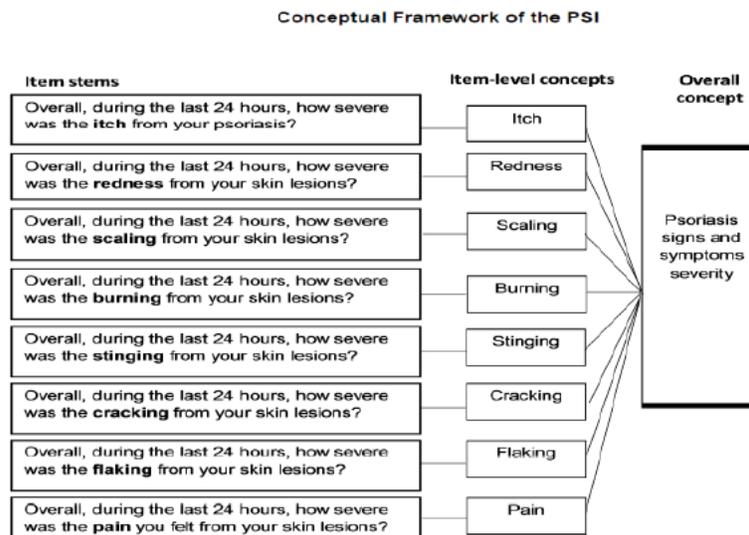
1.4 Labeling or promotional claim(s) based on the COA

The applicant's proposed labeling claims* for the PSI as described in the Summary of Clinical Efficacy are as follows:



2 CONCEPT OF INTEREST (COI) AND CONCEPTUAL FRAMEWORK

Below is an illustration of the conceptual framework for the Psoriasis Symptom Inventory:



Response options to each item stem listed in the conceptual framework:
0 = not at all severe, 1 = mild, 2 = moderate, 3 = severe, 4 = very severe

*Exact wording of labeling claims are not final and still in discussion.

Clinical Outcome Assessment Review

Yasmin Choudhry, M.D.

BLA 761032

Brodalumab

Psoriasis Symptom Inventory (Symptom severity)

3 CLINICAL OUTCOME ASSESSMENT (COA) MEASURE(S)

The Psoriasis Symptom Inventory (PSI): The PSI is an 8-item PRO measure intended to assess severity of the eight signs and symptoms (itch, redness, scaling, burning, stinging, cracking, flaking, and pain) of psoriasis. There are paper and electronic versions of the PSI. The recall period for the paper and electronic versions are 7-day and 24 hours, respectively. The PSI items are rated on a 5-point verbal response scale (0=not at all, 1=mild, 2=moderate, 3=severe, and 4=very severe).

Reviewer comment: The electronic version of the PSI (hand held electronic diary) was used for this drug development program.

Scoring algorithm: For each patient, the 8 individual item scores were summed to yield a PSI total score ranging from 0 to 32, with higher scores representing more severe signs and symptoms of plaque psoriasis.

- If a subject's response was missing for any single item on a given day, a PSI total score was not calculated for that particular day.
- For the 24-hour recall version of the PSI, a PSI weekly average score was calculated by summing the daily PSI total scores from the previous 7 days and dividing by the number of assessments available.
 - The PSI weekly average score was only calculated if there were at least 4 entries within the previous 7 days.
 - If a subject had multiple PSI entries on a single day, the most recent record from that day was used in computing the weekly average. If all records from the same date occurred at the same time, the entry with the worst response (highest score) was used in computing the weekly average.

4 CONTENT VALIDITY

The PSI was developed with a mixed methods approach (iterations of qualitative and quantitative methods). The qualitative phase consisted of a review of published literature and patient and clinician input. The quantitative phase comprised of item reduction using factor analysis.

This section provides a synopsis of the results from the mixed methods research. The study design and full findings are in the evidence dossier (Section 2 of the Evidence Dossier).

Concept elicitation interviews

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Focus-group interviews

Initially, five focus-group interviews were conducted by trained moderators with 39 patients with plaque psoriasis [8 mild defined as BSA > 3 ≤ 10 and PASI > 3 ≤ 10, and 31 patients with moderate to severe psoriasis defined as BSA > 10 and PASI > 10].

Among the moderate to severe psoriasis focus groups, 17 were women, average age of 45 years, 77% had at least a bachelor's degree. Ten subjects (~32%) in this group were married and an equal number had never been married; and 20 subjects (~65%) were working fulltime. While in the mild psoriasis group, 5 subjects were female, the average age was 36 years. The majority of participants was Caucasian and had completed at most some college, 50% were married, and 63% worked fulltime.

Below is a table that summarizes the most frequently reported signs and symptoms from the focus groups.

**Signs and Symptoms Most Frequently Cited in Concept Elicitation
Focus Groups (n = 39)**

Symptom Concept	Number of Patient Expressions of Concept	Percentage of All 263 Coded Symptom Expressions	Number of Focus Groups Contributing Concept Expressions (Total 5)
Itching	32	12	5
Scaling	24	9	5
Flaking	22	8	5
Tearing/cracking	19	8	4
Pain	18	7	3
Discomfort	17	7	4
Bleeding	15	6	4
Burning sensation	14	5	5
Other physical symptoms ^a	13	5	4
Dry skin	11	4	5
Inflammation	10	4	3
Skin tightness	8	3	2
Sensitivity to touch	6	2	3
Nail Pain/sensitivity	6	2	1
Stinging	4	2	3
Color	18	7	5
Other appearance ^b	11	4	5

^a Other physical signs/symptoms included: bruises/bruising, open sores, caused arthritis in the knee/arthritis type of situation crippled my hand, chills, hair loss/lose hair, overheated
Table 3 results are from Appendix C1: Initial Qualitative Research

Reviewer comment: FDA had questioned the interpretation of 'redness' by individuals with darker Fitzpatrick skin types as it was unclear whether redness will be interpreted as intended among patients with darker Fitzpatrick skin types who may demonstrate and report a different color of their psoriatic skin lesions (e.g., purple). FDA suggested that additional qualitative research should be provided to document the assertion that single word "redness" adequately covers the spectrum of coloration from red, to purple, to pink. Additionally, the FDA requested

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additional evidence to support the inclusion of pain in the PSI as the PRO dossier was internally inconsistent with regard to this symptom. The sponsor has addressed the FDA's concerns.

One-on-one interviews

An additional cross-sectional qualitative study with one-on-one 60-minute interviews was conducted in 20 adult patients (from US) in patients with BSA ≥ 10 , PASI ≥ 12 , and PGA ≥ 3 (moderate to severe psoriasis). Sixty-five percent of the enrolled patients (N = 13) were of the Fitzpatrick skin types (Mediterranean, dark brown and black) and had clinician-established Fitzpatrick scores of 4, 5, and 6.

Seventy percent of the participants reported “redness of skin lesions”. Patients described the color of their lesions in varying hues of red, regardless of skin tone. Other reported symptoms and signs in this study were itching (all 20 participants), scaling (75%), and pain (11%); the average rating of severity of pain due to skin lesions was 6.2 on a 10-point scale. Saturation was achieved for all concepts reported. Overall, subjects reported no difficulty with the comprehension of the terms ‘pain’ and ‘redness’, the remaining 6 PSI items, the 24 hour recall period and the response options.

Below is a table that summarizes the most frequently reported signs and symptoms from the one-on-one interviews.

Sub-Domains and Concepts	Number Patient Language Expressions Within Concept	% of Total Expressions (N = 792)	Number of Transcripts Contributing to Concept Expression	% of Transcripts Contributing (N = 20)
Skin Pain	90	11.4%		
General pain descriptions	41	5.2%	13	65.0%
Pain from scratching	22	2.8%	9	45.0%
Dull pain/ache/sore	5	0.6%	4	20.0%
Irritation	6	0.8%	4	20.0%
Stabbing/sharp pain	6	0.8%	4	20.0%
Other descriptions of pain	10	1.3%	6	30.0%
Itching, stinging, burning	154	19.4%		
Burning	29	3.7%	10	50.0%
Itching	109	13.8%	20	100.0%
Stinging	16	2.0%	8	40.0%
Heat	21	2.7%		
Heat	21	2.7%	9	45.0%
Stiffness, tightness	38	4.8%		
Stiffness	14	1.8%	7	35.0%
Tightness	24	3.0%	11	55.0%
Joint pain	34	4.3%		
Joint pain	34	4.3%	12	60.0%
Bleeding	38	4.8%		
Bleeding	38	4.8%	14	70.0%
Other sensation symptoms	33	4.2%		
Fatigue/low energy	16	2.0%	5	25.0%
Swelling	11	1.4%	4	20.0%
Other symptoms	6	0.8%	2	10.0%
Skin color	146	18.4%		
Color changes	119	15.0%	20	100.0%
Skin spotting	25	3.2%	8	40.0%
Redness from scratching	2	0.3%	2	10.0%
Cracking, flaking, scaling	190	24.0%		
Cracking	28	3.5%	10	50.0%
Flaking	70	8.8%	18	90.0%
Scaling	70	8.8%	17	85.0%
Raised skin	22	2.8%	10	50.0%
Lesions, plaque	48	6.1%		
Lesions	16	2.0%	9	45.0%
Plaque	24	3.0%	6	30.0%
Pustules	8	1.0%	4	20.0%

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Reviewer comment: The results demonstrate that all 8 concepts in the PSI (i.e., itch, redness, scaling, burning, stinging, cracking, flaking, and pain) were supported during the concept elicitation interviews.

Cognitive interviews

Based on the qualitative research, a pool of 14 candidate items was developed to address plaque psoriasis signs and symptoms severity, presence or absence of bleeding, and duration of symptoms. The 14-item draft version of the PSI was cognitively debriefed for instructions, item stems (questions), and response options in 20 patients (from Michigan, Washington, and Arkansas) with moderate to severe plaque psoriasis. The mean age of the sample was 48.8 years, 65% of the patients were male, 65% were Caucasian and the mean number of years since diagnosis was 17.9 (SD = 14.8). The mean baseline PASI score was 16.9 (SD = 4.1) and the mean baseline BSA affected was 18.1% (SD = 7.3%)/

The findings from the cognitive interviews indicated that severity was the most meaningful attribute of plaque psoriasis signs and symptoms. The burning/stinging item was identified by many patients as two separate concepts, and was therefore split into two individual items. Based on the input from the cognitive interviews, the resulting PSI contained 9-items including itch, redness, scaling, burning, cracking, stinging, flaking, pain, and bleeding. The average time to complete the diary was 3 minutes (range 2 to 10 minutes).

Qualitative Evidence Supporting Retained Concepts in the Draft PSI

Concept	Percent of Symptoms N = 263	Percent of Transcripts	Mean Importance	Mean Severity	Supported by Literature	Supported by Clinicians
Itch	13%	100	8.7	7.5	Yes	Yes
Pain	7%	60%	4.7	3.9	Yes	Yes
Burning	6%	80%	5.0	4.9	Yes	Yes
Stinging	2%	60%	5.7	7.0	Yes	Yes
Redness	12%	100%	9.1	7.4	Yes	Yes
Scaling	10%	100%	6.9	6.7	Yes	Yes
Cracking	8%	80%	8.3	7.9	Yes	Yes
Bleeding	6%	80%	7.7	5.1	Yes	Yes
Flaking	5%	100%	8.1	7.1	Yes	Yes

Importance scale: 0 (least important) to 10 (most important) determined by the patient

Severity scale: 0 (Not at all severe) to 10 (as severe as can be imagined) determined by the patient

Table 4 results are from [Appendix C1: Initial Qualitative Research](#)

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Item Reduction

The 9-item PSI was further revised to remove the item that assessed bleeding after completion of the quantitative study in 139 patients with moderate to severe plaque psoriasis. The rationale for removal of the bleeding item from the draft PSI was that bleeding is (in most cases) secondary to the core signs and symptoms of plaque psoriasis. Following the removal of the bleeding item, the exploratory principal component analysis (PCA) was conducted which indicated that the remaining 8 items (excluding the bleeding item) yielded a more unidimensional measure of the severity of plaque psoriasis signs and symptoms. Overall, the factor loadings for all the remaining 8 items were > 0.80 , and the total variance explained increased to 71%. Therefore, the resulting PSI focused on assessing the severity of eight plaque psoriasis signs and symptoms (i.e., itch, redness, scaling, burning, stinging, cracking, flaking, and pain).

Additional cognitive interviews

The 8-item PSI was debriefed in 10 additional cognitive interviews using a 24-hour recall period. The findings showed that patients understood and interpreted the final PSI instructions, item stems, response options, and recall period appropriately.

Reviewer comment: In summary, the sponsor has sufficiently established content validity of the PSI.

5 OTHER MEASUREMENT PROPERTIES (ITEM PERFORMANCE, RELIABILITY, CONSTRUCT VALIDITY, ABILITY TO DETECT CHANGE)

The measurement properties of the PSI were evaluated in the following three studies:

1. Study 20090619: Stand-alone observational study with exit interviews (n=139) - See the Evidence Dossier for details.
2. Study 20090062: Phase 2 clinical trial (n=186) – See the Evidence Dossier for details.
3. Study 20120102: Phase 3 clinical trial (n=661)

This section provides a synopsis of the psychometric results from the phase 3 brodalumab study (Study 20120102) since this is the only study that used the final 8-item PSI. The study design and population are described in Section C of this review. The full psychometric findings for all three studies are in the evidence dossier (Section 3 of the Evidence Dossier).

Item-level Analyses

At Baseline, patients used the entire range of the scale when responding to each item with the majority of patients reported “moderate” or “severe” experiences across all eight items. None of the items had floor effects (minimum response $>25\%$), with the percentage of individuals responding “not at all” for the eight items of the PSI ranging from 0.6% (flaking) to 13.9%

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(pain). There was also no evidence for ceiling effects (maximum response >25%), with the percentage of individuals responding “very severe” ranging from 12.2% (stinging) to 22.7% (flaking). Item-to-item correlations ranged from 0.51 [flaking and stinging] to 0.83 [stinging and burning] at Baseline, 0.74 [flaking and pain] to 0.90 [flaking and scaling] at Week 4, and 0.76 [pain and flaking] to 0.92 [stinging and burning] at Week 12. A correlation >0.80 was noted consistently across time points for burning and stinging (0.81 to 0.90) and scaling and flaking (0.81 to 0.92). Correlations between PSI items and the PSI total score ranged from 0.78 [redness] to 0.88 [burning] at Baseline, 0.89 [redness] to 0.94 [burning] at Week 4, and 0.90 [pain] to 0.95 [burning] at Week 12.

Reviewer comment: The item-item correlations for burning and stinging indicate that there may be some measurement redundancy. Similarly, the item-item correlations for scaling and flaking indicate potential measurement redundancy. However, based on the qualitative findings patients were able to distinguish between these concepts.

Reliability

Internal Consistency

The internal consistency reliability of the PSI appears adequate (Cronbach’s alpha >0.70).

Internal Consistency Reliability of the PSI at Baseline (Cronbach's Alpha), Single-day Scores

Item / Scale Score	N	Cronbach's α	
		Baseline	Baseline
Baseline	633	0.94	
1. Itch			0.93
2. Redness			0.93
3. Scaling			0.93
4. Burning			0.92
5. Stinging			0.93
6. Cracking			0.93
7. Flaking			0.93
8. Pain			0.93
Week 12	601	0.98	
1. Itch			0.97
2. Redness			0.98
3. Scaling			0.97
4. Burning			0.97
5. Stinging			0.97
6. Cracking			0.97
7. Flaking			0.98
8. Pain			0.98

Test-retest reliability

The test-retest reliability was evaluated at the following time points: Week 6 to Week 8, and Week 10 to 12. The test-retest reliability for these time points appear reasonable (ICC>0.80).

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Table 11. Test-retest Reliability Over 2-week Intervals Among Subjects With Stable Disease

	N	Mean (SD) Week 6	Mean (SD) Week 8	Difference ^a (SE)	t Value	p Value	ICC ^b
Stable subjects based on sPGA: week 6 to 8 ^c	461	10.57 (9.33)	10.45 (9.51)	0.12 (0.11)	1.07	0.28	0.97
Stable subjects based on the sPGA: week 10 to week 12 ^d	447	10.20 (9.76)	10.27 (9.93)	-0.07 (0.12)	-0.59	0.56	0.97
Stable subjects based on the sPGA and PASI: week 10 to week 12 ^e	219	8.20 (9.68)	8.35 (9.95)	-0.15 (0.13)	-1.14	0.26	0.98

^a Mean difference between specified 2 week intervals

^b ICC = Intraclass correlation coefficient

^c Stable defined as subjects that had the same sPGA score at week 6 and week 8

^d Stable defined as subjects that had the same sPGA score at week 10 and week 12

^e Stable defined as subjects that had the same sPGA and the same absolute PASI score at week 10 and week 12

Construct Validity

Convergent and Discriminant validity

Convergent validity was supported by moderate to strong correlation coefficients between the PSI total score and the skin-specific DLQI item 1 - “how itchy, sore, painful or stinging has your skin been” (0.69 to 0.86), the DLQI symptoms and feelings domain (0.66 to 0.87), and the SF-36 Bodily Pain domain (-0.58 to -0.61). Discriminant validity of the PSI total score was supported by small to moderate correlation coefficients between the PSI total score and the following divergent concepts: SF-36 role emotional (-0.31 to -0.39), role physical (-0.35 to -0.44), and vitality (-0.30 to -0.39) scores.

Known-groups Validity

The known groups validity was supported by significantly different PSI total scores across known PASI groups (< 12 vs ≥ 12; p < 0.001), sPGA groups (0 to 1 vs 2 to 3, vs 4 to 5; p < 0.001), DLQI groups (≤ 5 vs > 5; p < 0.001), and BSA groups (< 5, 5 to 10, > 10; p < 0.001) was supported by significantly different PSI total scores across known PASI groups (<12 vs ≥ 12; p < 0.001), sPGA groups (0 to 1 vs 2 to 3, vs 4 to 5; p < 0.001), DLQI groups (≤ 5 vs > 5; p < 0.001), and BSA groups (< 5, 5 to 10, > 10; p < 0.001).

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Known-Groups Validity of the PSI (Weekly Average) Total Scores Week 12 by PASI, sPGA, DLQI, and BSA Groups

	PSI Scores at Week 12 Mean (SD)	p-value
PASI Groups (N)		
< 12 (N = 383)	4.5 (5.1)	
≥ 12 (N = 216)	20.4 (8.0)	p < 0.001
sPGA Groups (N)		
0 to 1 (N = 274)	2.6 (3.3)	
2 to 3 (N = 201)	13.6 (8.5)	
4 to 5 (N = 124)	21.6 (7.5)	p < 0.001
DLQI Groups (N)		
≤ 5 (N = 350)	4.2 (4.9)	
> 5 (N = 242)	18.9 (8.6)	p < 0.001
BSA Groups (N)		
< 5 (N = 251)	2.9 (4.1)	
5 to 10 (N = 82)	7.2 (6.0)	
> 10 (N = 265)	18.1 (8.8)	p < 0.001

Ability to Detect Change

Mean changes in the PSI total scores from baseline to week 12 were significantly different among PASI groups ($p < 0.001$), and all pairwise comparisons were significantly different ($p < 0.001$), providing support for the ability of the PSI to detect change among subjects known to have had a change in clinical status.

Mean Change in the PSI (Weekly Average) Item and Total Scores from Baseline to Week 12 by PASI Improvement Status at Week 12

PSI Item and Total Score ^a	PASI Improvement Status at Week 12			p-value ^a
	PASI < 50 (n = 234) Mean (SD)	PASI 50 to < 75 (n = 49) Mean (SD)	PASI ≥ 75 (n = 295) Mean (SD)	
1. Itch	0.0 (0.9)	-1.3 (1.0)	-2.0 (1.0)	< 0.001
2. Redness	-0.1 (1.0)	-1.2 (1.1)	-1.9 (1.0)	< 0.001
3. Scaling	-0.1 (1.0)	-1.4 (1.1)	-2.2 (1.0)	< 0.001
4. Burning	-0.1 (1.1)	-1.3 (1.2)	-1.9 (1.1)	< 0.001
5. Stinging	0.0 (1.0)	-1.3 (1.2)	-1.7 (1.1)	< 0.001
6. Cracking	-0.1 (1.1)	-1.3 (1.2)	-2.0 (1.1)	< 0.001
7. Flaking	0.0 (1.0)	-1.4 (1.1)	-2.2 (1.0)	< 0.001
8. Pain	-0.1 (1.1)	-1.3 (1.2)	-1.7 (1.2)	< 0.001
PSI total score	-0.4 (7.3)	-10.6 (7.5)	-15.5 (7.2)	< 0.001

^a p-value is based on ANOVA model which includes PASI improvement status group as the independent variable and screening PSI (24 hour recall) item and total change scores as the dependent variable.

Mean change in the PSI total score from baseline to week 12 was also significantly different among sPGA groups ($p < 0.001$), providing additional support for the ability of the PSI to detect change among subjects known to have had a change in plaque psoriasis severity.

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Mean Change in the PSI (Weekly Average) Item and Total Scores from Baseline to Week 12 by sPGA Status at Week 12

PSI Item and Total Scores	sPGA Status at Week 12		p Value
	sPGA 0-1 (n=264) Mean (SD)	sPGA ≥ 2 (n=314) Mean (SD)	
1. Itch	-2.0 (1.0)	-0.3 (1.1)	< 0.001
2. Redness	-2.0 (1.0)	-0.4 (1.1)	< 0.001
3. Scaling	-2.2 (1.0)	-0.4 (1.2)	< 0.001
4. Burning	-1.9 (1.1)	-0.4 (1.3)	< 0.001
5. Stinging	-1.7 (1.1)	-0.4 (1.2)	< 0.001
6. Cracking	-2.0 (1.1)	-0.4 (1.3)	< 0.001
7. Flaking	-2.3 (1.0)	-0.4 (1.2)	< 0.001
8. Pain	-1.7 (1.2)	-0.4 (1.3)	< 0.001
PSI total score	-15.8 (6.9)	-3.2 (8.8)	< 0.001

6 INTERPRETATION OF SCORES

Treatment success was defined by a responder definition: a PSI total score of ≤ 8 with no item score > 1 .

Concordance was assessed between the responder definition and other measures of response to plaque psoriasis treatment. There was good agreement between the PSI responder definition and other clinical indicators of treatment success, including achieving a PASI 75 (kappa=0.69), PASI 90 (kappa=0.66) and sPGA 0 to 1 vs ≥ 2 (kappa=0.69). Below are the results of the agreement between the PSI responder definition and PASI response.

Concordance Between PSI Responder and PASI 50, PASI 75, PASI 90, and PASI 100 Response Thresholds at Week 12

	PSI (24 hour) ^a		Total, N (%)	Kappa (ASE)
	Responder, N (%)	Non-Responder, N (%)		
PASI 75 ^b				
Responder	234 (76.5)	72 (23.5)	306 (51.1)	0.69 (0.029)
Non Responder	22 (7.5)	271 (92.5)	293 (48.9)	
Total	256 (42.7)	343 (57.3)	599 (100.0)	
PASI 90 ^c				
Responder	196 (83.1)	40 (16.9)	236 (39.4)	0.66 (0.031)
Non Responder	60 (16.5)	303 (83.5)	363 (60.6)	
Total	256 (42.7)	343 (57.3)	599 (100.0)	
PASI 100 ^d				
Responder	120 (88.2)	16 (11.8)	136 (22.7)	0.45 (0.035)
Non Responder	136 (29.4)	327 (70.6)	463 (77.3)	
Total	256 (42.7)	343 (57.3)	599 (100.0)	

ASE Asymptotic Standard Error

^a Responder: PSI total score ≤ 8 without a score of > 1 on any PSI item; Non-responder: PSI total score > 8 or a score of > 1 on any PSI item

^b Responder: $\geq 75\%$ improvement from Baseline to Week 12 on the PASI; Non-responder $< 75\%$ improvement from Baseline to Week 12 on the PASI

^c Responder: $\geq 90\%$ improvement from Baseline to Week 12 on the PASI; Non-responder $< 90\%$ improvement from Baseline to Week 12 on the PASI

^d Responder: 100% improvement from Baseline to Week 12 on the PASI; Non-responder $< 100\%$ improvement from Baseline to Week 12 on the PASI

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7 LANGUAGE TRANSLATION AND CULTURAL ADAPTATION

The PSI was translated and is linguistically validated in 15 languages to date: Bulgarian, Czech, Dutch (Belgium, Netherlands), English (Australia, Canada, United Kingdom, United States), Estonian, French (Belgium, Canada, France, Switzerland), German (Germany, Switzerland), Greek, Hungarian, Italian, Latvian, Polish, Russian (Estonia, Latvia, Russia), Slovak, and Spanish (Mexico, Spain, United States).

Translations and cultural adaptations of the PSI were conducted in accordance with the methods described in the Principles of Good Practice for Translation and Cultural Adaptation, an International Society for Pharmacoeconomics and Outcomes Research (ISPOR) Task Force Report [†].

8 REFORMATTING FOR NEW METHOD OR MODE OF ADMINISTRATION

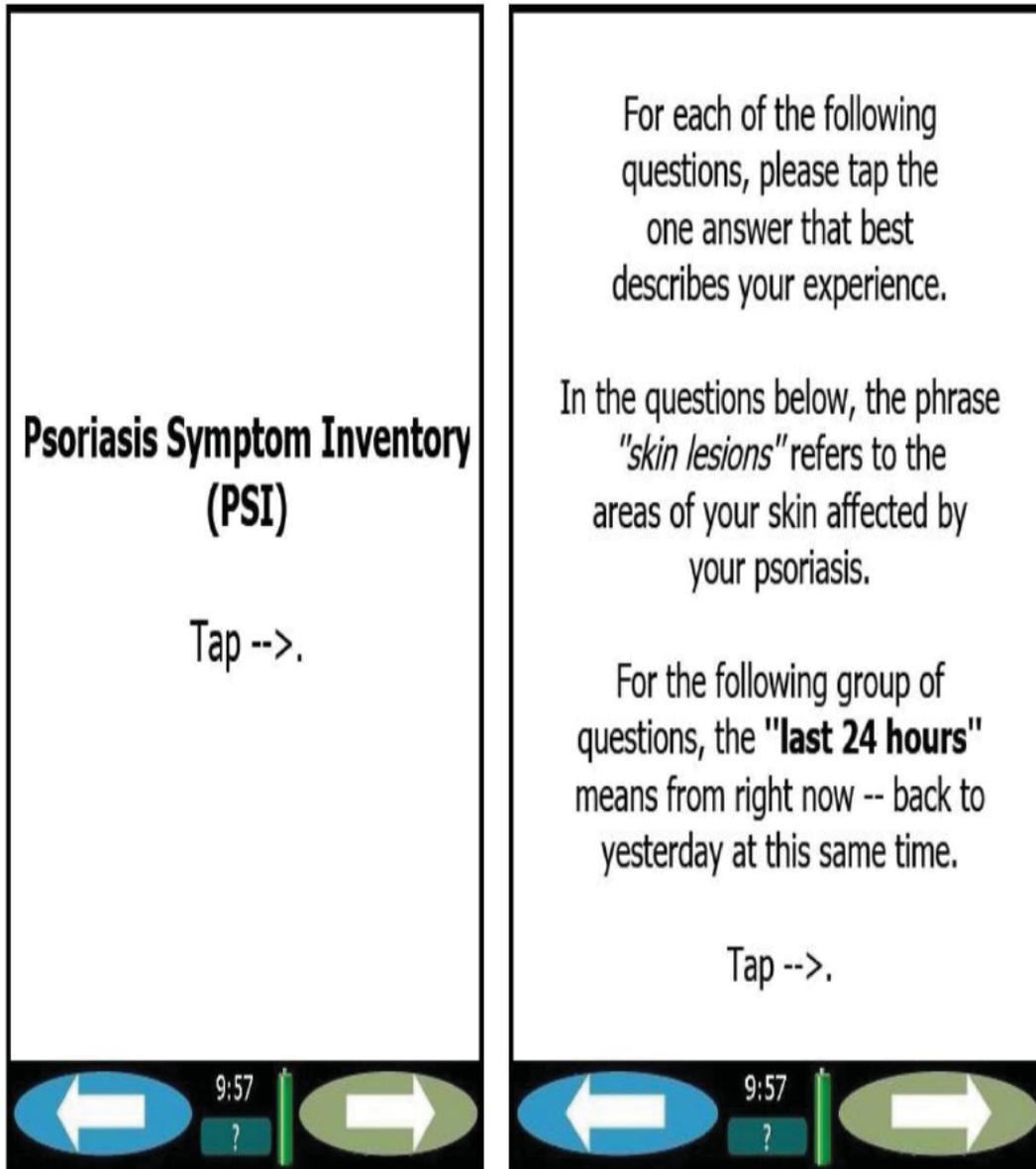
The PSI was developed for self-administration in pen-and-paper format. The conceptual and measurement equivalence between the paper and electronic versions of the 24-hour recall version of the PSI was demonstrated in a qualitative study (Appendix E of PRO evidence dossier). The findings from this study support a successful migration of the PSI from paper to electronic modes of administrations, specifically the personal digital assistant (PDA). The subjects' ability to successfully use the electronic version, as well as the consistent confirmation that the format changes did not impact the way subjects comprehended the PSI indicated that the migration of the PSI from paper to electronic administration was successful.

9 REVIEW USER MANUAL

A copy of the PSI user manual is in the PRO evidence dossier. The user manual includes the instrument, instructions for use, and scoring.

[†] Wild D et al: Multinational trials-recommendations on the translations, approaches to using the same language in different countries, and the approaches to support pooling the data: the ISPOR Patient-Reported Outcomes Translation and Linguistic Validation Good Research Practices Task Force report. *Value Health*. 2009;12(4):430-40.

Appendix A
Psoriasis Symptom Inventory (PSI)



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1) Overall, during the last 24 hours, how severe was the **itch** from your psoriasis?

Not at all

Mild

Moderate

Severe

Very Severe

9:57 ?

2) Overall, during the last 24 hours, how severe was the **redness** of your skin lesions?

Not at all

Mild

Moderate

Severe

Very Severe

9:57 ?

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3) Overall, during the last 24 hours, how severe was the **scaling** of your skin lesions?

Not at all

Mild

Moderate

Severe

Very Severe

9:57 ?

4) Overall, during the last 24 hours, how severe was the **burning** of your skin lesions?

Not at all

Mild

Moderate

Severe

Very Severe

9:57 ?

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5) Overall, during the last 24 hours, how severe was the **stinging** of your skin lesions?

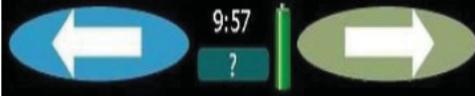
Not at all

Mild

Moderate

Severe

Very Severe



6) Overall, during the last 24 hours, how severe was the **cracking** of your skin lesions?

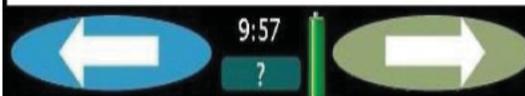
Not at all

Mild

Moderate

Severe

Very Severe



Clinical Outcome Assessment Review

Yasmin Choudhry, M.D.

BLA 761032

Brodalumab

Psoriasis Symptom Inventory (Symptom severity)

7) Overall, during the last 24 hours, how severe was the **flaking** of your skin lesions?

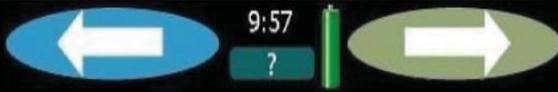
Not at all

Mild

Moderate

Severe

Very Severe



8) Overall, during the last 24 hours, how severe was the **pain** you felt from your skin lesions?

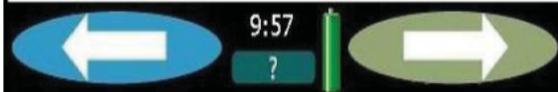
Not at all

Mild

Moderate

Severe

Very Severe



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

/s/

YASMIN A CHOUDHRY
07/12/2016

SELENA R DANIELS
07/12/2016

ELEKTRA J PAPADOPOULOS
07/12/2016



Memorandum

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
DIVISION OF CARDIOVASCULAR AND RENAL PRODUCTS

Date: June 30, 2016

From: Fred Senatore, MD, PhD, FACC
Medical Officer
Division of Cardiovascular and Renal Products / CDER

Through: Norman Stockbridge, MD, PhD
Division Director
Division of Cardiovascular and Renal Products / CDER

To: Strother D. Dixon, RPM, ODE III, DDDP
Cc: Gary Chiang MD Medical Officer, ODE III, DDDP

Subject: DCRP consult to help DDDP determine the risk of major adverse cardiac events (MACE) with the product brodalumab.

This memo responds to your consult to us requesting that we help DDDP determine the risk of major cardiovascular adverse events (MACE), defined as cardiovascular death, MI, or stroke with the product brodalumab. DDDP stated “based on the 120 day safety update data, 23 treatment emergent fatal events were reported in brodalumab subjects in the psoriasis subset. The most common deaths among brodalumab subjects were Cardiac disorders (8 deaths with at least 4 under acute MI)”. DCRP received and reviewed the following materials:

- Your consult request dated April 8, 2016
- BLA 761032 (section 2.4 nonclinical overview; section 2.5 clinical overview)
- REMS Oversight Committee presentation dated April 20, 2016
- MACE statistical analysis of the 120-day safety update data performed by the Division of Biometrics #7 received June 8, 2016.

Background

AstraZeneca submitted a BLA for brodalumab, an IgG monoclonal antibody IL-17A receptor inhibitor, for the treatment of moderate to severe plaque psoriasis. Brodalumab has also been developed for other indications: rheumatoid arthritis, psoriatic arthritis, asthma, and Crohn's Disease. The drug product binds to the IL-17 receptors and therefore increases serum cytokine IL-17A. It is not clear how the increased level of IL-17A would affect the rates of cardiovascular and cerebrovascular events in the presence of impaired binding to the IL-17A receptor. DDDP was concerned that the 8 cardiovascular deaths reported in the 120-day safety update in conjunction with brodalumab-mediated increases in serum IL-17A levels reflected a risk of MACE with brodalumab.

Reviewer's Comment: A literature search for the role of IL-17A in and the impact of interfering with the signaling pathway of this interleukin on cardiovascular disease was unrevealing. The role of IL-17A in cardiovascular disease remains poorly understood (SU, 2013).

Nonclinical

Brodalumab was administered once weekly to cynomolgus monkeys (study 107714) for up to 6 months at NOAEL exposure multiples ranging from 47-111-fold the clinical exposure at a 210 mg dose administered q 2 weeks. There were 4 dosing groups: # 1 (6 male and 6 female) receiving vehicle control; # 2 (4 male and 4 female) receiving 10 mg/kg/dose; #3 (4 male and 4 female) receiving 25 mg/kg/dose; and #4 (6 male and 6 female) receiving 90 mg/kg/dose. ECG examinations were conducted pre-dose and approximately 72 hours post-dose during study week 1 (study day 4) and study week 25 (study day 172). In male monkeys, there were no changes in ECG parameters (RR, QRS, PR, QT, and QTc intervals) from pre-dose to both day 4 and day 172 for any doses. The mean heart rate, however, increased from a pre-dose of approximately 152 bpm to 168, 175, and 182 bpm for group # 2, 3, and 4, respectively, on day 4. The mean heart rate returned to baseline on day 172. In female monkeys, there were no changes in ECG parameters as well as mean heart rate from pre-dose to both day 4 and day 172. Microscopic changes in the heart after brodalumab treatment at necropsy showed evidence of degeneration/necrosis and lymphocytic and macrophage infiltrates in one male monkey in the control group, and 3 female monkeys (1 in the control group and 2 in group # 4).

Reviewer Comment: The ECG and histopathology results in the cynomolgus monkey model were unremarkable. The significance of what appeared to be a dose-dependent increase in heart rate in male monkeys on day 4 is not clear. I did not see a cardiac safety signal in this pre-clinical study that may portend cardiovascular risk in the clinical program.

Clinical Pharmacology

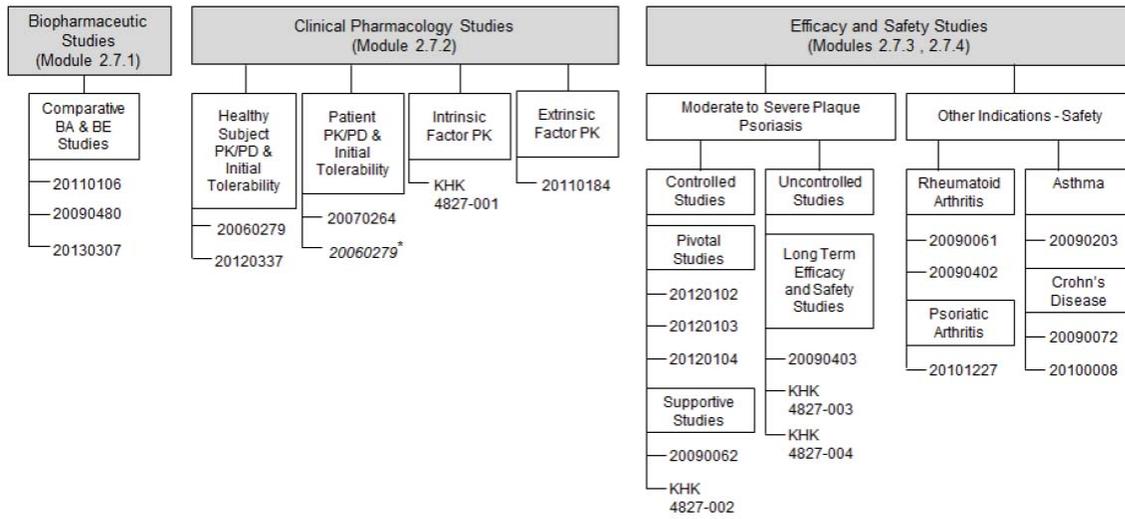
Brodalumab exhibited nonlinear kinetics and an estimated bioavailability of 55% using PK modeling meta-analysis. The predicted t_{\max} after subcutaneous administration of brodalumab 210 mg was approximately 3 days. Following multiple SC administrations of 210 mg q 2 weeks, the effective half-life of brodalumab was 11.7 days using the accumulation ratio, and 10.9 days using population PK modeling. The median time to steady-state was 70 days. After discontinuation of a steady-state dosing regimen of 210 mg q 2 weeks, population PK simulation predicted that serum brodalumab concentrations below the quantification limit in 95% of subjects 63 days after discontinuation. Body weight was a significant predictor of brodalumab clearance and distribution.

Reviewer Comment: The PK data appeared to support the dosing of 210 mg q2W.

Clinical

The development program for brodalumab is shown in Figure 1. A total of five indications were pursued: psoriasis, psoriatic arthritis, rheumatoid arthritis, asthma, and Crohn's disease involving 23 studies. Across all indications, 5205 subjects received brodalumab, representing 5903.7 subject-years. This exposure came from subjects in Phase 2 and Phase 3 studies: 20090061 and 20090402 (rheumatoid arthritis), 20090072 and 20100008 (Crohn's disease), 20090203 (asthma), 20101227 (psoriatic arthritis), 20090062, 20090403, 20120102, 20120103, and 20120104 (psoriasis).

Figure 1. Studies supporting the psoriasis indication



Source: Section 2.5 Clinical Overview

Note: study 20060279 under clinical pharmacology is listed twice in this figure because it contained healthy subjects and psoriasis patients.

Of the 5205 subjects exposed to brodalumab, 4461 subjects with psoriasis were exposed to brodalumab with dosing and duration distributed as follows: 1291 subjects (brodalumab 210 mg q2W, 1471.5 subject-years), 279 subjects (brodalumab 140 mg q 2W, 302.7 subject-years), 2327 subjects (variable dosing unspecified, 3364.6 subject-years), and 564 subjects (210 mg q 2W after ustekinumab, 310.0 subject-years).

The patients described in the paragraph above included 1549 subjects who were exposed to brodalumab in the Phase 3 pivotal studies. These patients were distributed as follows: 476 subjects (brodalumab 210 mg q 2W, 535.3 subject-years), 119 subjects (brodalumab 140 mg q2W, 128.2 subject-years), 750 subjects (variable dosing unspecified, 966.0 subject-years) and 204 subjects (brodalumab 210 mg q2W after ustekinumab, 118.2 subject-years).

Studies with brodalumab are briefly described:

Healthy Subjects

Phase 1 Studies:

- **BE/20090480** was a multicenter open label randomized 2-period cross-over trial enrolling 141 healthy subjects evaluating a single dose of brodalumab 210 mg SC pre-filled syringe vs. Pen bioequivalence. There was one SAE and there were 3 subjects with elevated creatinine phosphokinase classified as ischemic heart disease. A review of ECG data in the cohorts did not reveal a safety signal.
- **BE/20130307** was a multicenter open label randomized 2-period crossover trial enrolling 80 healthy subjects evaluating brodalumab 210 mg SC pre-filled syringe 1.5 mL vs 0.5 mL bioequivalence, safety and tolerability. There were no SAEs and no events classified as ischemic heart disease. A review of the ECG data did not reveal a safety signal.
- **PK/20110106** was a single center open label randomized crossover trial enrolling 80 healthy subjects evaluating brodalumab 140 mg SC investigating auto injector devices. There were no SAEs and no ECG safety signal.
- **PK/20120337** was a single-center open label 2-period crossover trial enrolling 27 healthy subjects evaluating brodalumab 140 mg SC single dose on day 1 and day 22. There were no SAEs and no ECG safety signals.

Rheumatoid Arthritis

Phase 1 Studies

No Phase 1 reported in Rheumatoid Arthritis.

Phase 1b / 2a Studies:

- **PK/20070264** was a multicenter double blind randomized placebo-controlled ascending multiple dose trial enrolling 40 subjects with active rheumatoid arthritis concurrently treated with methotrexate. Brodalumab doses were 50, 140, 210 mg SC q2W for 10 weeks or brodalumab 420 or 700 mg IV q4W days 1 and 29 (2 doses). There were 3 SAEs (complicated migraine, GI reflux, and non-cardiac chest pain). There were no cardiac events.

Phase 2 Studies

- **Efficacy/Safety 20090061** was a multicenter double blind randomized placebo-controlled multiple dose study in 252 subjects with active rheumatoid arthritis. They received brodalumab 70, 140, or 210 mg SC q2W (day 1 to week 10) or placebo. The results were negative for efficacy. There were 5 SAEs including 1 fatality. The

facility was a 57 year old white female with a history of tobacco abuse, hypertension, depression, hyperlipidemia, obesity and multiple concomitant medications. There were no ECG abnormalities. She died in her sleep from cardiopulmonary failure. None of the other SAEs were cardiac. The ECG database was unremarkable.

- **Efficacy/Safety 20090402** was a multicenter open label extension to study 20090061 in 211 subjects with rheumatoid arthritis, treated with brodalumab 210 mg SC q2W (day 1 to week 262) + methotrexate. The study was prematurely terminated due to lack of efficacy. There were no reported treat-related serious adverse events. There were 8 adverse events, none were cardiac.

Phase 3 Studies

No Phase 3 studies reported in patients with rheumatoid arthritis.

Psoriatic Arthritis

Phase 1 Studies

No Phase 1 studies reported in patients with psoriatic arthritis.

Phase 2 Studies

- **Efficacy/Safety 20101227** was a multicenter double blind randomized placebo controlled study with an open label extension in 168 subjects with psoriatic arthritis. In the double-blind portion, subjects received brodalumab 140 mg or 280 mg SC q2W (day 1 to week 10) or placebo. In the open label extension, subjects received brodalumab 280 mg SC q2W from weeks 12 to 252. This study is currently ongoing. A review of the database as of cut-off January 2015 showed 4 SAEs in the double blind period (n=56) in the 140 mg arm, 4 SAEs in the double blind period (n=56) in the 280 mg arm and no SAEs in the placebo arm (n=52). All these SAEs were classified as infection/infestation (6 SAEs) and neoplasm-breast cancer (2 SAES). There were 323 non-serious treatment emergent adverse events in the double blind period (84 in the placebo arm, 119 in the 140 mg arm, and 120 in the 280 mg arm). Of these, 1 non-serious AE was classified as cardiac (i.e. palpitations) in the 280 mg arm. No further information was available on this AE. The CSR did not have tabulated ECG data.

Phase 3 Studies

No Phase 3 studies reported in patients with psoriatic arthritis.

Asthma

Phase 1 Studies

No Phase 1 studies were reported in patients with asthma.

Phase 2 Studies

- **Efficacy/Safety 20090203** was a multicenter double blind randomized placebo-controlled dose ranging study in subjects with inadequately controlled asthma. Subjects were randomized to receive placebo or brodalumab 140, 210, or 280 mg SC q2W (day 1 to week 10). The results showed no efficacy. There were 7 SAEs (1 on placebo {n=76}, 3 on 140 mg {n=74}, 1 on 210 mg {n=76}, 2 on 280 mg {n=76}). These were classified as infectious. There were no cardiac SAEs. Of 140 non-serious AEs, 1 was classified as cardiac (i.e. palpitations) in the 210 mg arm. No further information was available on this AE. A review of the ECG data (i.e. various intervals) was unrevealing.

Phase 3 Studies

No Phase 3 studies reported in patients with asthma.

Crohn's Disease

Phase 1 Studies

No Phase 1 studies reported in patients with Crohn's disease.

Phase 2 Studies

- **Efficacy/Safety 20090072** was a multicenter double blind randomized placebo controlled trial in 130 subjects with Crohn's disease. Subjects were randomized to brodalumab 210, 350, or 700 mg IV (day 1 to week 4) in a study that was planned for 12 weeks. The study was terminated due to lack of efficacy. There were 2 SAEs in 2 subjects on placebo, 5 SAEs in 3 subjects at the 210 mg dose, 18 SAEs in 5 subjects at the 350 mg dose, and 12 SAEs in 7 subjects at the 700 mg dose. All the SAEs were gastrointestinal related to Crohn's disease. There were no reported cardiac SAEs.
- **Efficacy/Safety 20100008** was a multicenter open label extension to study 20090072 in 67 subjects with Crohn's disease. They were scheduled to receive

brodalumab 350 mg IV q4W (day 1 to week 128) but the study was terminated due to lack of efficacy. There were 15 SAEs but no fatalities. The SAEs were related to Crohn's disease. There were no reported cardiac SAEs.

Phase 3 Studies

No Phase 3 studies reported in patients with Crohn's disease.

Moderate to Severe Plaque Psoriasis

Phase 1 Studies

- **PK/20060279** was a Part A (healthy subjects, n=58) / Part B (stable psoriasis, n=26) multicenter randomized double-blind placebo-controlled ascending single dose study evaluating brodalumab at 7, 21, 70, 210 or 420 mg SC. There were no clinically significant adverse events and no ECG based safety signal.
- **PK/KHK 4827-001** was a two-part study. Part A was a multicenter randomized single blind placebo-controlled single ascending dose study. Brodalumab at doses of 70,140, 210, or 420 mg SC or brodalumab 210 mg IV were administered to healthy males (n=40). Part B was a multicenter open label non-controlled ascending single-dose study. Brodalumab at doses of 140 or 350 mg SC were administered to subjects with psoriasis (male or female not specified, n=13). There were no SAEs. There were no cardiac adverse event reports and the ECGs were normal.
- **DDI/PK/20110184** was a multicenter open label single dose study of 21 subjects with psoriasis evaluating the interaction between brodalumab 210 mg SC single dose with midazolam. In a separate cohort, brodalumab 140 mg SC single dose was evaluated in 10 subjects with psoriasis. There were no SAEs and no ECG signal.

Phase 2 Studies

- **Efficacy/Safety 20090062** was a multicenter randomized double-blind placebo controlled multiple dose trial of 198 subjects with psoriasis receiving brodalumab at doses of 70, 140, or 210 mg SC q2W (day 1 to week 10) or brodalumab 280 mg SC q4W (day 1 and weeks 4 and 8) or placebo q2W (day 1 to week 10). There were 3 SAEs (neutropenia, renal colic, and ectopic pregnancy). There were no ECG abnormalities or cardiac disorders.
- **Efficacy/Safety 20090403** was a multicenter open label extension of study 20090062. There were 181 subjects receiving brodalumab 210 mg SC q2W (week 0

to week 358). Subjects \leq 100 kg had doses decreased to 140 mg. If response was inadequate, a rescue dose of 210 mg was permitted. Most subjects had a treatment emergent adverse event (n=171 of 181). There were 20 serious adverse events in 15 subjects with 3 SAEs classified as cardiac (atrial fibrillation, congestive heart failure, and supraventricular tachycardia). There was one fatality (subject 96266006016) due to rupture of an abdominal aortic aneurysm. The 3 cardiac SAEs are briefly described:

- The subject experiencing atrial fibrillation was a 63 year old white female who had a pre-existing history of atrial fibrillation and experienced a worsening of this condition, requiring admission to a hospital to control the ventricular rate. The ECG on admission was a-flutter with a 2:1 block.
- The subject with supraventricular tachycardia (SVT) was a 51 year old white female who had a pre-existing history of SVT. The SVT event occurred while the subject was hospitalized for a common bile duct stone. Initial vagal maneuvers did not resolve the SVT but later in the hospitalization, it was reported to have resolved.
- The subject with congestive heart failure was a 30 year old (difficult to read the subject's age because of smudge in the screen and printed image) white female who experienced congestive heart failure in the setting of streptococcal necrotizing fasciitis with septic shock and aggressive fluid management. The heart failure resolved.
- **Efficacy/Safety KHK 4827-002** was a multicenter double blind randomized placebo-controlled trial of 151 Japanese subjects with psoriasis receiving placebo or brodalumab at doses of 70, 140, or 210 mg SC q2W (weeks 0 to 10). There was 1 myocardial infarction in the 70 mg arm as the only cardiac event. This was a 69 year old male with a history of tuberculosis and a long history of smoking who experienced myocardial infarction. The patient underwent PCI with stent placement. There was no other history.

Supportive Phase 3 Studies

- **Efficacy/Safety KHK 4827-003** was an open label completion of the Phase 2 study KHK 4827-002 involving 145 of the original 151 Japanese subjects. The subjects in this study were those who did not experience a treatment-related serious adverse event that led to discontinuation from the previous study. Therefore, this was an enriched population. Subjects in this study were treated with brodalumab 140 mg or 210 mg SC q2W (weeks 0 to 50). This study was supportive of efficacy showing positive results as measured by Psoriasis Area Severity Index (PASI) score. In

addition to the single myocardial infarction reported in the double blind -002 Phase 2 study, there were 2 additional cardiac events both on placebo: palpitations and supraventricular extrasystoles. It is not clear if these occurred in the same patient.

- **Efficacy/Safety KHK 4827-004** was an open label study of 30 Japanese subjects with pustular psoriasis or psoriatic erythroderma, treated with brodalumab 140 or 210 mg SC q2W (weeks 0 to 50). The results of this trial supported efficacy for brodalumab using the primary endpoint Clinical Global Impression, with a score of “improved” or “remission” in 29 of the 30 subjects. There was no top-line data on dose response. A total of 28 subjects experienced an adverse event, 5 were serious (none were cardiac). There was one cardiac non-serious adverse event report of ventricular extrasystoles.

Reviewer Comment: At this point of the review that included all except the 3 pivotal phase 3 trials to support the psoriasis indication, I did not see a risk of major adverse cardiac events from both the non-clinical program and the clinical program for the 5 indications. The next three Phase 3 studies that formed the basis of the BLA for the psoriasis indication are described in more detail herewith.

Pivotal Phase 3 Studies

Three Phase 3 pivotal clinical trials serving as the basis of efficacy for the psoriasis indication were AMAGENE-1 (study 20120102), AMAGINE-2 (study 20120103) and AMAGINE-3 (study 20120104). All three studies were conducted simultaneously:

- AMAGENE-1: initiated August 29, 2012 and cut-off date March 12, 2014
- AMAGENE-2: initiated August 22, 2012 and cut-off date September 22, 2014
- AMAGENE-3: initiated September 11, 2012 and cut-off date August 30, 2014

At the initial design of the Phase 3 trials, an independent Data Monitoring Committee was established and a charter was approved to review unblinded data for the entire phase 3 program. A Cardiovascular Events Committee (CEC) (Duke Clinical Research Institute) was also deployed to adjudicate any major adverse cardiac event that could be reported as per the CEC charter.

Reviewer Comment: The rationale for the establishment of a CEC was not made clear in the BLA package. There were no indications from the preclinical and early clinical studies that there was a risk of cardiovascular events. I believe that concerns about serum IL-17A elevations as a mechanistic pathway towards adverse cardiac events was hypothetical based on published studies, thus prompting the establishment of a CEC.

All of the Phase 3 pivotal psoriasis studies included a placebo-controlled double-blind 12-week induction phase followed by a double-blind maintenance phase of 40 weeks totaling 52 weeks. Following 52 weeks, there was an open-label long term extension of up to 271 weeks. For all 3 studies, there was a re-randomization at the week 12 visit. Original and re-randomized treatment assignments remained blinded until all subjects reached week 52 or withdrew from the study.

AMAGENE-1

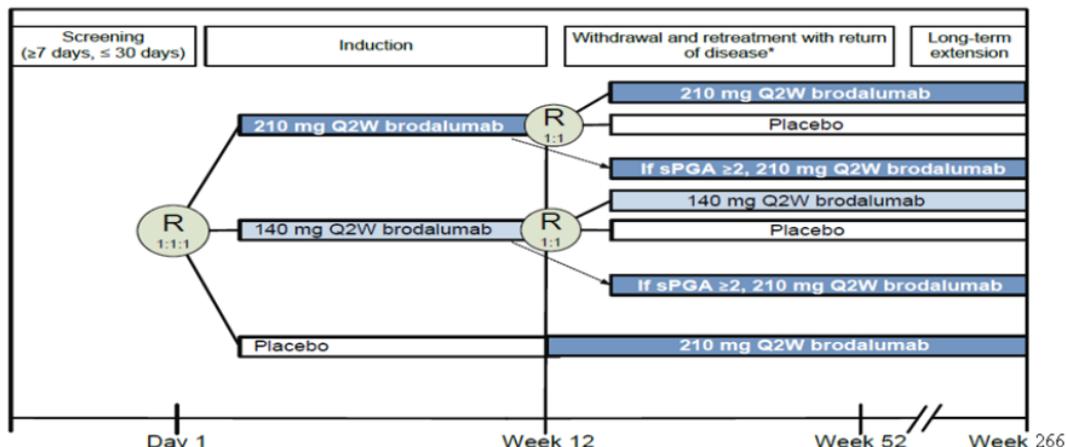
The design of the AMAGENE-1 study is shown in Figure 2. Subjects were randomized 1:1:1 to receive study drug (brodalumab 210 mg, brodalumab 140 mg, or placebo) SC q2W with an additional loading dose at week 1. At week 12, subjects originally randomized to either of the brodalumab arms who had success as defined by the static Physician's Global Assessment (sPGA-score 0 or 1) were re-randomized to placebo or continued brodalumab at their induction dose. This was called the withdrawal and retreatment phase in order to determine the effect of withdrawal on sPGA. Placebo subjects and subjects who did not qualify for re-randomization based on sPGA were assigned to brodalumab 210 mg q2W (i.e., not re-randomized). Re-randomized subjects who had a return of the disease (sPGA \geq 3) from week 16 through week 52 initiated retreatment at the original induction dose. After 12 weeks of re-treatment, subjects with inadequate response (sPGA \geq 3 or persistent score of 2 over a 4 week period) could qualify for rescue treatment with brodalumab 210 mg q 2W.

A total of 661 subjects were randomized to AMAGENE-1 (222 to brodalumab 210 mg q2W, 219 to brodalumab 140 mg q2W, and 220 to placebo). Most subjects were white males with a mean age of 46 years. During the 12 week induction phase, 33 subjects discontinued from the study. At week 12, 628 subjects entered the withdrawal phase; 283 subjects were re-randomized and 345 were not re-randomized. Fifty-five non re-randomized subjects and 7 re-randomized subjects discontinued from the study during the withdrawal phase, and 149 subjects entered the re-treatment phase. An additional 6 subjects discontinued the study during the re-treatment phase and 2 subjects discontinued during the rescue phase. A total of 558 subjects continued in the open label extension after week 52. Sometime between week 12 and week 52, the placebo subjects (n=12) received brodalumab, but the timing of this was not displayed.

The results of AMAGENE-1 demonstrated efficacy as measured by Psoriasis Area Severity Index (PASI).

Figure 2. AMAGENE-1 (Study 20120102) Design

Figure 2 Study 20120102 study design and treatment schema



R Randomization; Q2W Every 2 weeks (with an additional loading dose 1 week after initiation of brodalumab); sPGA Static Physician's Global Assessment. Subjects received investigational product subcutaneously at day 1; weeks 1, 2, 4, 6, 8, 10, 12, 13, 14; and every other week.

Subjects who did not attend their week-12 visit did not receive any further investigational product.

* Subjects could qualify for retreatment with their induction dose with a single sPGA of ≥ 3 at or after week 16; see Section 16.1.1 of Study 20120102 for further details on criteria for retreatment (return of disease). Subjects received 3 weekly doses followed by every other week doses upon experiencing return of disease at or after week 16. If a subject had return of disease through week 52, he or she received treatment at his or her initially randomized dose (if originally randomized to brodalumab) or 210 mg Q2W (if originally randomized to placebo).

Subjects could qualify for rescue treatment after at least 12 weeks of retreatment with inadequate response (defined as persistent sPGAs of 2 over at least a 4 week period or a single sPGA ≥ 3). See Section 16.1.1 of Study 20120102 for further details.

After the blind to original and rerandomized treatment assignment had been broken, an analysis to identify the most appropriate maintenance dose(s) of brodalumab was performed. Based upon the results of that analysis, an amendment could be pursued to change the dose and/or frequency in some or all subjects.

Source: Module 2.7.3, Figure 1.

Source: Applicant's eCTD Module 2.5, Figure 2

AMAGENE-2 and AMAGENE-3

The design of AMAGENE-2 and AMAGENE-3 were the same and is shown in Figure 3. Subjects were randomized 2:2:1:1 to receive brodalumab 210 mg q2W, brodalumab 140 mg q2W, ustekinumab 45 mg for subjects ≤ 100 kg and 90 mg for subjects > 100 kg at week 1 and week 4, and placebo during the 12 week induction period with an additional loading dose at week 1. At week 12, subjects received maintenance treatment as follows:

- Subjects originally randomized to any brodalumab were re-randomized 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.
- Subjects originally randomized to placebo were assigned to brodalumab 210 mg q2W.

Rescue treatment with brodalumab 210 mg for inadequate response could occur at week 16 for all poor-responders, including those on ustekinumab. After week 16 through week 52, subjects on brodalumab were rescued with brodalumab 210 mg q2W. Subjects on ustekinumab remained on ustekinumab. At week 52, subjects originally randomized to ustekinumab were assigned to brodalumab 210 mg q2W. All other subjects continued on their maintenance treatment.

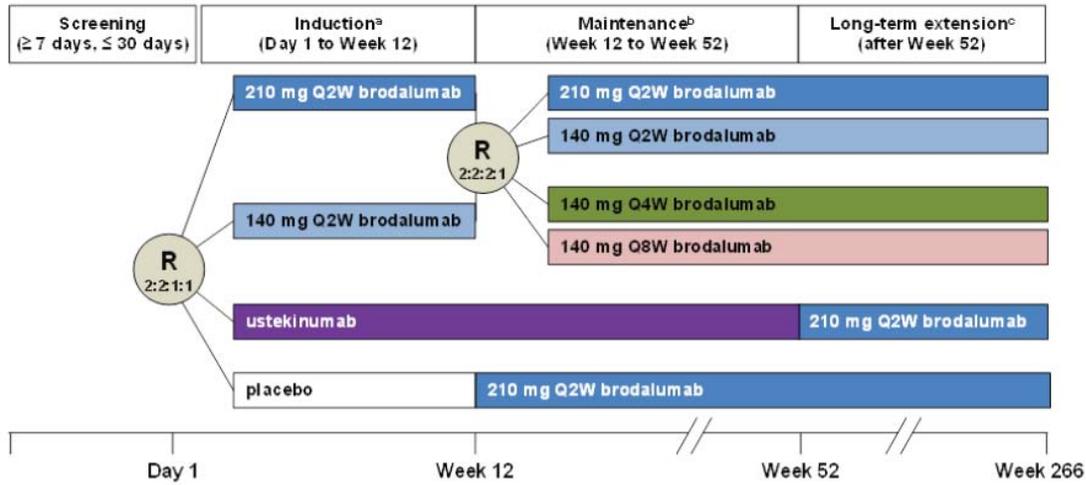
For AMAGENE-2, a total of 1831 subjects (induction phase: 309 placebo, 300 ustekinumab, 610 brodalumab 140 mg q2W, and 612 brodalumab 210 mg q2W) were randomized. Most subjects were white males with a mean age of 45 years. At week 12, 1760 subjects entered the maintenance phase (re-randomized subjects: 334 brodalumab 210 mg q2W, 337 brodalumab 140 mg q2W, 335 brodalumab 140 mg q4W, and 168 brodalumab 140 mg q8W; non-re-randomized subjects: 289 ustekinumab/ustekinumab and 297 placebo/brodalumab 210 mg q2W). Twenty-nine non-randomized subjects and 44 re-randomized subjects discontinued during the maintenance phase. A total of 833 subjects were rescued through week 52. A total of 1601 subjects continued in the open label extension after week 52.

For AMAGENE-3, a total of 1881 subjects (induction phase: 315 placebo, 313 ustekinumab, 629 brodalumab 140 mg q2W, and 624 brodalumab 210 mg q2W) were randomized into the study. Most subjects were white males with a mean age of 45 years. At week 12, 1799 subjects entered the maintenance phase (re-randomized subjects: 324 brodalumab 210 mg q2W, 343 brodalumab 140 mg q2W, 341 brodalumab 140 mg q4W, and 174 brodalumab 140 mg q8W; non-re-randomized subjects: 301 ustekinumab/ustekinumab and 298 placebo/brodalumab 210 mg q2W). Twenty-nine non-re-randomized subjects and 32 re-randomized discontinued during the maintenance phase. A total of 827 subjects were rescued through week 52. A total of 1656 subjects continued in the study after week 52.

The results of both studies demonstrated efficacy as measured by Psoriasis Area Severity Index (PASI).

Figure 3. AMAGENE-2 (study 20120103) and AMAGENE-3 (study 20120104) designs

Figure 3 Studies 20120103 and 20120104 study design and treatment schema



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.

Subjects qualified for rescue treatment at or after week 16 according to the rules in each study protocol.

Source: Module 2.7.3, Figure 2.

Source: Applicant's eCTD module 2.5, Figure 3

Major Adverse Cardiac Events in all studies

The number of MACE in the first 12 weeks of the three placebo-controlled double blind pivotal trials is shown in Table 1. There were only 3 events (2 myocardial infarctions and 1 stroke) in the brodalumab 140 mg q2W arm.

Table 1. Occurrence of MACE through initial 12 weeks in 3 Phase-3 placebo controlled trials

Type of MACE	Placebo (N=842) n (%)	Ustekinumab (N=613) n (%)	Brodalumab		
			140 mg q2W (N=1452) n (%)	210 mg q2W (N=1456) n (%)	All (N=2908) n (%)
Numbers of subjects reporting MACE	0	0	3 (0.2)	0	3 (0.1)
Cardiovascular deaths	0	0	0	0	0
Myocardial Infarction	0	0	2 (0.1)	0	2 (0.1)
Stroke	0	0	1 (0.1)	0	1 (<0.1)

Source: REMS Oversight Committee Presentation April 20, 2106, same in eCTD section 2.7.4 Summary of Clinical Safety

Between weeks 12 and 52, there were substantial numbers of subjects who were not re-randomized or who were rescued, thereby raising a question about the integrity of the double-blindness during the maintenance phase of the pivotal phase 3 programs. After week 52, the exposure to brodalumab dropped considerably. Of the original 4461 subjects with psoriasis exposed to brodalumab, only 166 continued to be exposed for 2 years or greater. The exposure dropped from 122 at month 48 to zero at 60 months from trial initiations (section 2.7.4 summary of clinical safety-table 10).

A review of adjudicated MACE from the database listed 9 adjudicated cardiovascular deaths. A listing of these subjects, including the induction dose, number of doses and dosing sequence, and time between last dose and death, are shown in Table 2. The subjects' ages ranged from 24 to 75 years (mean age 51.8 years). Six of the nine cardiovascular deaths were adjudicated as sudden death (5 on brodalumab and 1 on ustekinumab). The number of brodalumab doses received before sudden death, summed from induction, maintenance, and rescue phases, ranged from 8 to 32. The duration of time between the last dose of brodalumab and sudden death ranged from 0 to 87 days. One subject on ustekinumab experienced sudden death after 2 doses of ustekinumab. The time from last dose of ustekinumab to sudden death was 13 days.

Table 2. List of adjudicated cardiovascular deaths

Study #	Subj ID	Age (years)	Sex	Cause of Death	Drug: Induction Dose	# Induction Doses and Dosing Sequence	Time between last dose and death (days)
20120102	10266009012	71	M	Stroke	B: 210 mg q2W	7→rerandomized to P: 6 doses→ resumed B: 9 doses	(b) (6)
20120102	10266042001	75	M	Sudden Death	B: 210 mg q2W	7→rerandomized to B: 8 doses	
20120103	10311001011	39	M	Stroke	B: 210 mg q2W	7 (no re-randomization)	
20120103	10348006032*	40	M	-----	B: 140 mg q2W	7→rerandomized to B 140 mg q8W: 5 doses→ rescued with B 210 mg: 5 doses	
20120103	10366053011	60	M	Sudden Death	U	2	
20120103	10366084031	24	F	Sudden Death	P	7→ assigned to B 210 mg: 8 doses	
20120104	10448006003	54	M	Sudden Death	B: 210 mg q2W	7→rerandomized to B 140 mg q8W: 1 dose→ rescued with B 210 mg: 24 doses	
20120104	10466046008	66	M	Sudden Death	B: 140 mg q2W	7→rerandomized to B 210 mg: 14 doses	
20120104	10466068006	37	M	Sudden Death	B: 210 mg q2W	7→rerandomized to B 140 mg q4W: 1 dose→ rescued with B 210 mg: 7 doses	

Source: Reviewer analysis of database; B = brodalumab; P = placebo; U =ustekinumab

**Subject 10348006032 was documented in the database to have an adjudicated sudden cardiac death but was not listed in the ISS as a death. Further investigation of the database showed that this subject had 4 SAEs: 3 psoriasis exacerbations and 1 liver-toxicity, all resolved. There was a discrepancy in the BLA database regarding this subject.*

In addition to psoriasis, the medical histories of those subjects adjudicated to have had a cardiovascular death are as follows:

- Subject 10266009012: 71 year old white male with a history of hypertension, arrhythmia, hypothyroidism, sleep apnea, and a 50 pack-year smoking history. The subject died of a stroke. The time from last dose of brodalumab to death was (b) (6) days.
- Subject 10266042001: 75 year old white male with a history of hypertension, hypercholesterolemia, diabetes mellitus, obesity, left bundle branch block and coronary artery disease with coronary bypass surgery. The subject experienced sudden death at home. Efforts to revive him were unsuccessful. There was no autopsy. The time from last dose of brodalumab to death was (b) (6) (b) (4), (b) (6) days.
- Subject 10311001011: 39 year old white male with a history of alcohol abuse, anxiety, depression, psychological disorders-unspecified and psoriatic arthritis. The subject died of a stroke. The time from last dose of brodalumab to death was (b) (6) days.
- Subject 10348006032: 40 year old white male with a history of tobacco abuse and alcohol abuse. Although the database documented this patient to have an adjudicated sudden death, the subject listing in the ISS described this subject as having exacerbation of psoriasis and liver toxicity, all resolved. There is a discrepancy in the database.
- Subject 10366053011: 60 year old white male with a history of arthritis, myocardial infarction, congestive heart failure, and hypercholesterolemia. The subject experienced sudden death at home while with his wife. Emergency medical services were unable to resuscitate him. There was no autopsy. The time from last dose of ustekinumab to death was (b) (6) days.
- Subject 10366084031: 24 year old white female with a history of depression, anxiety, insomnia, alcohol abuse, seizure disorder, personality disorder, and drug abuse. She had flu like symptoms and lower back pain before sudden death. On autopsy, her blood was positive for only antihistamine and negative for commonly abused drugs. Physical findings included petechiae and Tardieu type spots (ecchymoses that follow death by strangulation or suffocation) on the face, neck and upper chest. There were no anatomical findings. The cause of death was listed as undetermined. The time from last dose of brodalumab to death was (b) (6) days.

- Subject 10448006003: 54 year old white male with a history of hypertension, hypercholesterolemia, and hiatal hernia. The subject experienced sudden death at home. No autopsy was performed. The time from last dose of brodalumab to death was (b) (6) days.
- Subject 10466046008: 66 year old white male with a history of hypertension, diabetes mellitus type 2, and 15-pack year smoking history. The subject experienced sudden death in his sleep. No autopsy was performed. The time from last dose of brodalumab to death was (b) (6) days.
- Subject 10466068006: 37 year old white male with a history of hyperlipidemia, type 2 diabetes mellitus, morbid obesity (464 pounds), past smoker (pack-years unknown), gastric esophageal reflux disease, chronic obstructive pulmonary disease, migraines, disc herniation, and poor dentition. The subject developed new onset atrial fibrillation and discontinued participation from the study. The subject experienced sudden death at his home determined to be caused by cardiomyopathy. The time from last dose of brodalumab to death was (b) (6) days.

The high number of sudden deaths in relatively young subjects raised concern about drug causality. The medical histories of subjects who had sudden death contained cardiac disorders including cardiac arrhythmia, cardiac disease with history of previous MI and heart failure, cardiac risk factors portending cardiovascular disease, and seizure disorder that may have contributed to sudden death. There was also an implication of possible suicide in the 24 year old WF. The high variability in both the number of brodalumab doses and the duration of time from the last dose of brodalumab to the time of cardiovascular death, including sudden death, made assessment of drug causality difficult.

A review of adjudicated MACE from the database listed 21 adjudicated myocardial infarctions. A listing of these subjects, including a brief medical history, the induction dose, number of doses and dosing sequence, and time between last dose and MI, are shown in Table 3 located in the Appendix of this document. The subjects' ages ranged from 37 to 70 years (mean age 57.2 years). The number of brodalumab doses received before MI, summed from induction, maintenance, and rescue phases, ranged from 4 to 31. One subject on ustekinumab experienced an MI after 3 doses. The duration of time between the last dose of brodalumab and MI ranged from 0 to 13 days. The time from last dose of ustekinumab to MI was 68 days. None of the MI events reported arrhythmic complications, and all were associated with coronary artery disease.

In general, the subjects who sustained an MI had a medical history that predisposed them to this event. However, in the case of a 38 y/o WM with no previous medical history except psoriasis (subject 10266012007), there was a low probability that he would have sustained an MI. However, diagnostic angiography revealed 2-vessel disease. This subject may have had silent coronary artery disease.

The high variability in both the number of brodalumab doses and the duration of time from the last dose of brodalumab to the time of myocardial infarction made assessment of drug causality difficult.

The exposure-adjusted rate of MACE in brodalumab-exposed subjects, defined as the total number of subjects who experienced MACE (from day 1 to the end of follow-up) divided by the duration of exposure x100, was 0.6 per 100 subject-years. This number was similar to that found in a systematic review of psoriasis and MACE (Armstrong, 2013).

DCRP Comments

- Data from both preclinical and clinical studies for other potential indications: rheumatoid arthritis, psoriatic arthritis, asthma, and Crohn's disease, did not show a cardiovascular safety signal suggesting a risk of MACE with brodalumab. Non-pivotal supportive psoriasis trials also did not show a risk of MACE with brodalumab.
- A review of hemodynamic parameters in the pivotal phase 3 psoriasis program (i.e. blood pressure, heart rate) revealed no notable changes that portended an increase in cardiovascular risk. Data from hemodynamic tables from all three phase 3 psoriasis trials showed systolic blood pressures in the 120 mmHg range and diastolic blood pressures in the 80 mmHg range throughout the course of the study at the pre-specified timepoints of measurement. Similarly, pulse rates were maintained in the range of 70 beats per minute.
- In the three pivotal studies for the psoriasis indication, the 12-week induction period was the only phase of these studies where a double-blind comparison could be made between two doses of brodalumab, active comparator (ustekinumab) and placebo. In this phase, there were only 3 MACE events in the lower dosing arm of brodalumab (140 mg q2W). The number of events was insufficient to draw a conclusion about the risk of MACE with brodalumab.
- Beyond the 12-week induction period, there was significant unblinding due to non-rerandomization assignments and rescue. Beyond 52 weeks in the open label extension period, there was considerable reduction in the number of subjects reported to continue in the trial. This compromised the analysis of MACE between brodalumab and comparators beyond 12 weeks. The high variability in the number of brodalumab doses, and the duration of time from the last dose of brodalumab to the time of MACE made assessment of drug causality difficult. In my opinion, lumping all the MACE occurrences in this setting for the purpose of evaluating drug-related risk was uninformative.
- The exposure-adjusted incidence rate of MACE in brodalumab-exposed subjects for the entire follow-up period (i.e. 266 weeks based on the original design of the studies) was 0.6 per 100 subject-years. A systematic review and meta-analysis of observational studies of mild to severe psoriasis and MACE was conducted by Armstrong et al (2013). Nine studies were examined, representing a total of 201,239 patients with mild psoriasis and 17,415 patients with severe psoriasis. The incidence rate of myocardial infarction for mild and severe psoriasis ranged from 0.17 to 0.4 per 100 subject-years and the incidence of cardiovascular mortality for severe psoriasis ranged from 0.3 to 1.6 per 100 subject-years. In the same meta-analysis, the incidence of stroke for mild and severe psoriasis ranged

from 0.4 to 0.5 per 100 subject-years for patients with mild psoriasis, and 0.6 to 0.7 per 100 subject-years for patients with severe psoriasis. The authors of the meta-analysis concluded that mild-severe psoriasis was associated with an increased risk of myocardial infarction and stroke. Severe psoriasis was also associated with an increased risk of cardiovascular mortality. The incidence rate of MACE in brodalumab-exposed patients with moderate to severe psoriasis was similar to that found in the meta-analysis. Other studies have suggested an association between psoriasis and cardiovascular disease based on similar pathology and mechanistic links between these two diseases (Golden, 2013). Based on this, I could not conclude that the occurrences of MACE in the pivotal phase 3 trials were attributable to brodalumab.

- The assessment of sudden death in 6 of the 9 adjudicated cardiovascular deaths listed in the database (5 on brodalumab and 1 on ustekinumab) was concerning, especially when the subjects who died were young. A thorough review of the patient records showed histories of cardiovascular disease, including risk factors for cardiac disease that could have contributed to an arrhythmic sudden death. My investigation of the relationship between psoriasis and sudden death led to a study by Simsek et al. (2013) who evaluated P-wave dispersion (PWD) and QT dispersion (QTD) in patients with psoriasis. PWD is an ECG marker used to evaluate the risk of atrial arrhythmias. QTD can be used to assess homogeneity of cardiac repolarization and may be a risk for ventricular arrhythmias. The authors concluded that both PWD and QTcD (QTD corrected by Bazett's formula) were increased in psoriasis patients compared to healthy subjects. These markers, however, have not been clinically correlated to arrhythmic events. In the brodalumab trials, a thorough QT/QTc analysis was not performed. The Phase 1 data showed no relationship between QT, QTcF (QT interval corrected using Fridericia's formula) and serum brodalumab levels over a range of concentrations from 50 to 300,000 ng/mL (studies 20060279 and 20070264). Based on 1) the medical history of the subjects who had sudden death, 2) the suggestion that patients with psoriasis might be at risk for arrhythmias, and 3) no noted brodalumab-mediated ECG repolarization abnormalities in the phase 1 studies, I could not conclude that brodalumab caused sudden death.

DCRP Conclusion

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.

References

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Appendix

Table 3 Description of Subjects adjudicated to have experienced a Myocardial Infarction

Study #	Subj ID	Brief Medical History other than Psoriasis	Drug: Induction Dose	# Induction Doses and Dosing Sequence	Time between MI and last dose (days)
20120102	10216007023	65 y/o WM w/ho HTN, obesity, T2DM, CKD, diabetic neuropathy, COPD, GERD, TIA, vitamin B12 deficiency, renal lithiasis.	B: 210 mg q2W	7→rerandomized to P: 3 doses→ resumed B: 19 doses	(b) (6)
20120102	10266012007	38 y/0 WM, with no medical history, experienced angina. Angiography showed 2-vessel CAD and had PCI/stent.	P	7→assigned to B: 11 doses	
20120102	10266018008	57 y/o WM w/ho HTN, CAD with h/o stent placement, DM.	B: 210 mg q2W	7→rerandomized to B 210 mg: 4 doses	
20120102	10266048003	61 y/o WM w/ho HTN, PVD, hyperlipidemia, T2DM, diabetic neuropathy, COPD, 2 pk per day smoking (duration unknown).	P	7→assigned to B: 4 doses	
20120103	10348008015	66 y/o WM w/ho CAD, CABG, HTN, hyperlipidemia, obesity.	B: 140 mg q2W	7→rerandomized to B: 140 mg q4W: 3 doses→rescued with B: 19 doses	
20120103	10348009002	65 y/o WM w/ho HTN, ARRYTHMIA, AAA, right iliac artery aneurysm, T2DM, kidney stones, thyroid goiter.	B: 140 q2W	7→rerandomized to B 140 mg q4W: 4 doses	
20120103	10348009044	62 y/o WM w/ho suspected MI, syncope, ACS, HTN.	B: 140 mg q2W	7→rerandomized to B 240 mg: 24 dose	
20120103	10366024010	50 y/o WM w/ho RBBB, HTN, tobacco abuse.	U	Remained on ustekinumab	
20120103	10366037005	59 y/o WM w/ho obesity, sleep apnea, GERD, anxiety, restless leg syndrome.	B: 140 mg q2W	7→rerandomized to B 140 mg q8W: 2 doses	

20120103	10366059017	59 y/o WM w/ho HTN, obesity.	B: 140 mg q2W	7→rerandomized to B 210 mg: 19 doses
20120103	10366064006	57 y/o WM w/ho HTN, arrhythmia, atrial fibrillation, COPD, CAD, CABG, morbid obesity.	B: 140 mg q2W	6
20120103	10366069004	37 y/o ("race other") M w/ho hyperlipidemia, HTN, arrhythmia, CAD, palpitations, syncope, angina, smoker.	B: 210 mg q2W	7→rerandomized to B 140 mg q8W: 1 dose→rescued with B: 11 doses
20120103	10366081012*	56 y/o WF w/ho HTN, angina pectoris, CHF, CAD, MI, hypercholesterolemia, T2DM, anxiety.	B: 210 mg q2W	7→rerandomized to B 140 mg q4W: 1 dose→rescued with B: 4 doses
20120104	10448008028	51 y/o W with h/o HTN, impaired glucose tolerance, 15 pack year history smoking.	B: 210 mg q2W	6→rerandomized to B: 140 mg q2W: 18 doses
20120104	10448019023	63 y/o WM w/ho HTN.	P	7→assigned to B: 17 doses
20120104	10466013008	58 y/o WM w/ho hypercholesterolemia, HTN, obesity, hyperlipidemia, tobacco abuse, remote h/o cocaine.	B: 140 mg q2W	7→rerandomized to B: 140 mg q2W: 3 doses→rescued with B: 11 doses
20120104	10466029002	46 y/o WM w/ho HTN, migraines, paresthesia, alcohol abuse, smoking. Angiography showed 99% RCA lesion→stent placed.	B: 140 mg q2W	4
20120104	10466031002	57 y/o WM w/ho MI, obesity, HTN, smoking, alcohol abuse.	B: 210 mg q2W	6→rerandomized to B: 140 mg q4W: 3 doses→rescued with B: 9 doses
20120104	10466046012	70 y/o WF w/ho HTN, anxiety, dyspepsia, chronic back pain, migraine..	B: 140 mg q2W	7→rerandomized to B: 210 mg: 23 doses
20120104	10466052003	63 y/o WM w/ho HTN, hyperlipidemia, T2DM, peripheral neuropathy, cerebral ischemia,	B: 140 mg q2W	7→rerandomized to B: 210 mg: 18

(b) (6)

		cerebral atrophy, past alcohol abuse.		doses	(b) (6)
20120104	10466054010	61 y/o WM w/ho HTN, hypercholesterolemia, anxiety, depression, GERD, obesity, past smoker.	B: 140 mg q2W	7→rerandomized to B: 140 mg q4W: 2 doses	

Review of database; AAA = abdominal aortic aneurysm; ACS: acute coronary syndrome; B = brodalumab; CABG: coronary artery bypass graft; CAD =coronary artery disease; CHF = congestive heart failure; CKD =chronic kidney disease; COPD =chronic obstructive lung disease; GERD: gastro-esophageal reflux disease; HTN =hypertension; P = placebo; PVD = peripheral vascular disease; RBBB = right bundle branch block; RCA =right coronary artery; T2DM =type 2 diabetes mellitus; U =ustekinumab; WF = white female; WM =white male; w/ho = with history of..;

**Subject 10366081012 was adjudicated to have a myocardial infarction but the ISS listing specified atrioventricular block as the SAE rather than an MI. There was a discrepancy in the database regarding this subject.*

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/s/

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