FDA Briefing Document

Dermatologic and Ophthalmic Drugs Advisory Committee Meeting

July 19, 2016

Background Package for BLA 761032
Siliq (brodalumab) injection, 210 mg/1.5 ml

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
OFFICE OF NEW DRUGS
DIVISION OF DERMATOLOGY AND DENTAL PRODUCTS

DISCLAIMER STATEMENT

The attached package contains background information prepared by the Food and Drug Administration (FDA) for the panel members of the advisory committee. The FDA background package often contains assessments and/or conclusions and recommendations written by individual FDA reviewers. Such conclusions and recommendations do not necessarily represent the final position of the individual reviewers, nor do they necessarily represent the final position of the Review Division or Office. We have brought Siliq (brodalumab) injection, 210 mg/1.5 ml to this Advisory Committee in order to gain the Committee's insights and opinions. The background package may not include all issues relevant to the final regulatory recommendation, but instead is intended to focus on issues identified by the Agency for discussion by the advisory committee. The FDA will not issue a final determination on the issues at hand until input from the advisory committee process has been considered and all reviews have been finalized. The final determination may be affected by issues not discussed at the advisory committee meeting.

Table of Contents

Division Director Memorandum

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation III
Division of Dermatology and Dental Products
M E M O R A N D U M

Date: June 22, 2016

From: Kendall A. Marcus, MD
Director, Division of Dermatology and Dental Products
Office of Drug Evaluation III, CDER, FDA

To: Chair, Members and Invited Guests
Dermatologic and Ophthalmic Drugs Advisory Committee (DODAC)

Subject: Overview of the July 19, 2016 DODAC meeting

Siliq (brodalumab) injection, 210 mg/1.5 ml for the treatment of adults with chronic moderate to severe plaque psoriasis who are candidates for systemic therapy or phototherapy

Division Director Memo

A biologics licensing application (BLA) was submitted for SILIQ (brodalumab) for the treatment of moderate to severe plaque psoriasis in adults who are candidates for systemic therapy or phototherapy. Brodalumab is a monoclonal antibody (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 product will be given by prefilled syringe (PFS) for subcutaneous administration at 210 mg (140 mg/mL, 1.5 mL PFS) at 0, 1, and 2 weeks with subsequent doses administered every two weeks (Q2W).

In support of this application, the product sponsor submitted three Phase 3 clinical trials and a single Phase 2 clinical trial in psoriasis subjects. The clinical program also included product quality, pharmacology/toxicology, and clinical pharmacology data to support marketing of the biologic product and additional data from clinical trials for other indications.

The efficacy of brodalumab for the treatment of psoriasis is supported by the three pivotal Phase 3 placebo-controlled clinical trials; two of these trials also included an ustekinumab comparator arm. 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 $\geq$12, static Physician's Global Assessment (sPGA) score of at least 3, and body surface area (BSA) involvement $\geq$10% at baseline. In all trials, both brodalumab doses were superior to placebo ($p<0.001$) for the co-primary endpoints (PASI 75 and sPGA of 0 or 1) as well as the secondary endpoints (PASI 100, sPGA of 0, and Psoriasis Symptom Inventory (PSI)) at Week 12. For the comparison of brodalumab and ustekinumab, brodalumab 210 mg was superior to ustekinumab ($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 occurring in the Phase 3 clinical trials. A total of 6 completed suicides in all brodalumab clinical trials were reported (4 in psoriasis, 1 in rheumatoid arthritis, and 1 in psoriatic arthritis); however, one suicide was later adjudicated as indeterminate due to possible accidental drug overdose. The Phase 3 clinical trials were terminated early by the sponsor, thereby preventing further assessment of safety. A comprehensive evaluation of suicidal ideation and behavior (SIB) was undertaken by both the product sponsor and the Agency and will be discussed at length during this Advisory Committee meeting.

In addition to SIB safety issues, the increase in IL-17 that results from IL-17 receptor blockade could theoretically affect cardiovascular outcomes and major cardiovascular adverse events. It has been hypothesized that IL-17 receptor inhibition may lead to an increase in other cytokines involved in inflammation thereby resulting in an increase in MACE events. Review of the clinical trial data by the Division of Cardiology and Renal Products (DCRP) did not support a direct association of brodalumab with MACE given the small number events observed during the relatively brief placebo-controlled periods of the Phase 3 trials. In addition, review of the available literature is unclear in regards to the mechanistic action through which brodalumab could increase MACE risk. The evaluation of brodalumab use and MACE events will also be a focus of the Advisory Committee meeting.

In summary, this new biologic product under review for the treatment of chronic plaque psoriasis acts as an IL-17A receptor blocker in the cytokine cascade. The biologic effects of the resulting increase serum IL-17A and its interaction with other cytokines are not well understood; however, the available data raise concerns about a potential interaction with cytokines in the central nervous system and an impact on cardiovascular atherosclerosis. Limited controlled data in the brodalumab development program for these uncommon events makes the assessment of risk-benefit for brodalumab challenging. The Division of Dermatology and Dental Products (DDDP) is seeking input from the Advisory Committee regarding the benefit to risk balance for brodalumab.

The safety review of this application involved eight Divisions in the Center for Drug Evaluation and Research. Within the Office of New Drugs, DDDP, DCRP, the Division of Psychiatry Products and the Division of Biostatistics 7 conducted reviews of the available safety data. Within the Office of Surveillance and Epidemiology, the Division of Epidemiology, the Division of Pharmacovigilance and the Division of Risk Management also conducted safety evaluations, as did the Division of Clinical Pharmacology 3 from the Office of Clinical Pharmacology. Diverse opinions were formed about the risk-benefit assessment of brodalumab. Because of the different emphases of each review, the diversity of opinions of the reviewers, and in the spirit of equal voice, all Divisions have contributed sections to this background document summarizing their reviews and conclusions in lieu of providing a single comprehensive safety summary. As you read this briefing package, you may find it helpful to orient yourself to the organization by referencing the Table of Contents.

I. INTRODUCTION

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

Available approved systemic treatments for moderate to severe psoriasis in candidates for systemic therapy or phototherapy are described in Table 1 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	**Year approved**	**Class**	**Warnings/Precautions**
Acitretin	1996*	retinoid	teratogen; hepatotoxicity; hyperostosis; lipid effects
Methotrexate	1953*	folate antagonist	teratogen; liver fibrosis/cirrhosis; hematologic toxicity; interstitial pneumonitis; opportunistic infections
Cyclosporine	1995*	inhibits IL-2	hypertension; nephrotoxicity; serious infections; malignancy
Apremilast	2014	phosphodiesterase 4 inhibitor	depression; weight decrease; drug-drug interactions
Biologic Therapies			
Etanercept	2004	TNFa-blocker	serious infections (including TB); malignancy; central nervous system demyelinating disorders; hematologic events (pancytopenia); reactivation of hepatitis B; autoimmunity
Infliximab	2006	TNFa-blocker	serious infections (including TB); malignancy; demyelinating disease; hepatotoxicity
Adalimumab	2007	TNFa-blocker	serious infections (including TB); malignancy; reactivation of hepatitis B; demyelinating disease; hematologic reactions (pancytopenia); autoimmunity
Ustekinumab	2009	Interleukin-12 and -23 antagonist	serious infections; malignancy; reversible posterior leukoencephalopathy syndrome
Secukinumab	2015	Interleukin-17A antagonist	serious infections; TB, exacerbation of Crohn's, hypersensitivity
Ixekizumab	2016	Interleukin-17A antagonist	infection, hypersensitivity, exacerbation of Crohn's

* Therapies may not have been initially approved for psoriasis
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.

Brodalumab (previously AMG-827), is 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 (Figure 1). The IgG2 antibody is expressed in a Chinese Hamster Ovaries (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

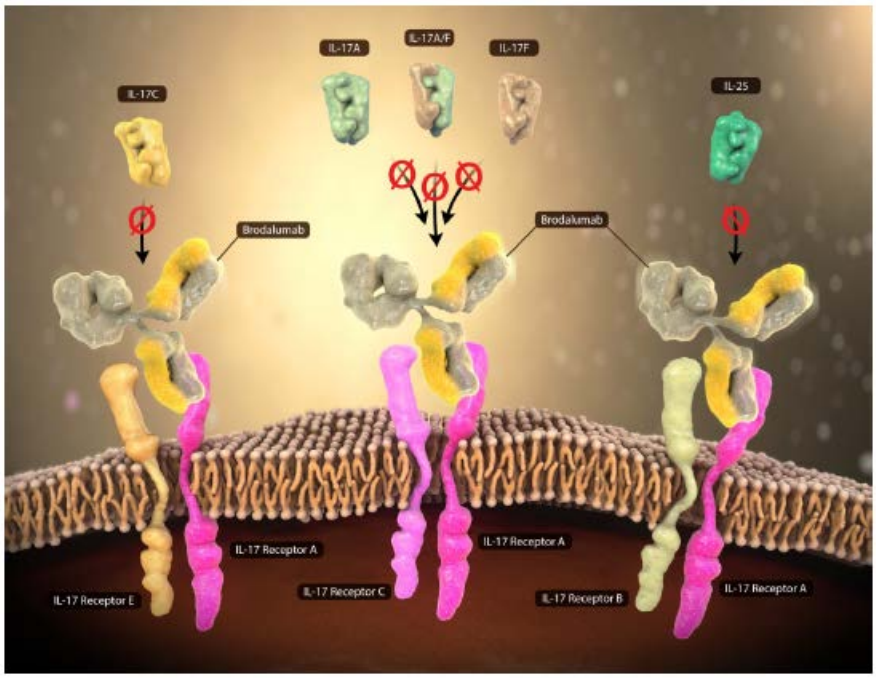
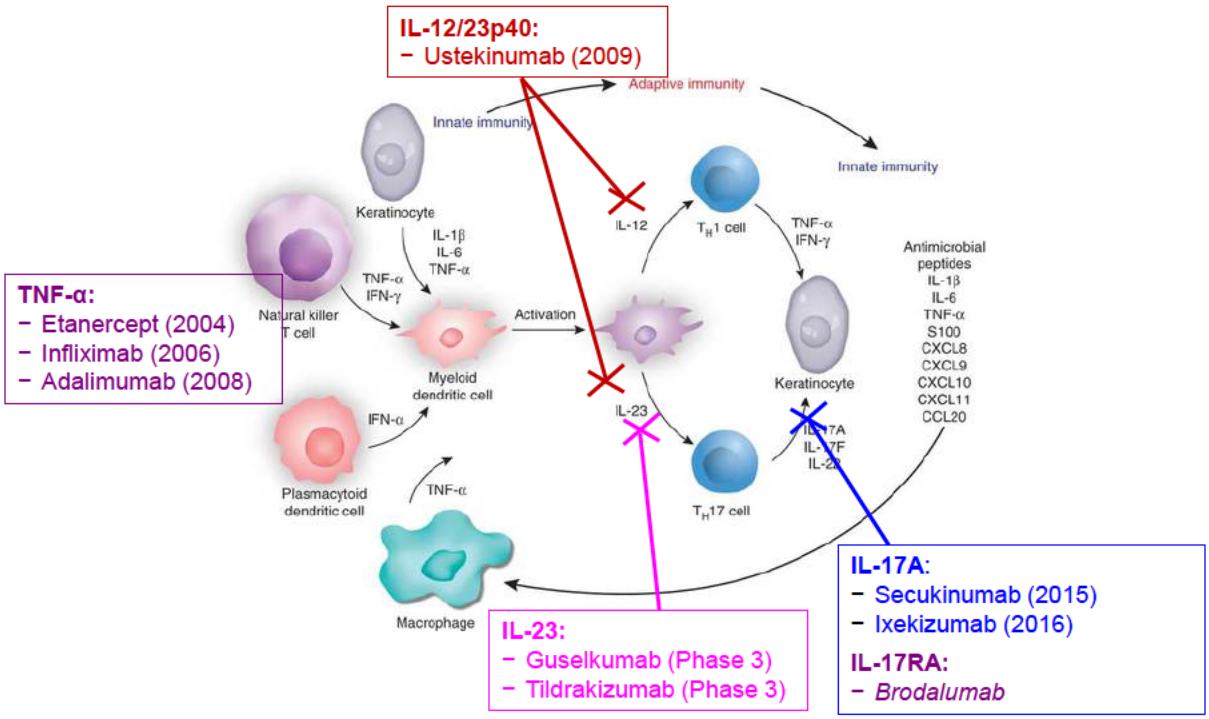


Figure: Adopted from Applicant's submission

Figure 1 represents the targets within the cytokine network of the currently approved biologics as well as those in Phase 3 development for the treatment of psoriasis.

Figure 2: Cytokine Targeting of Biologics for Plaque Psoriasis. Figure adopted and reconstructed from literature *Nature Biotech*, 2011(29): 614-625.



Note: Dates reflect approval of psoriasis indication and are not indicative of the date of original approval of biologic.

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

Table 2: Synopsis of Clinical Trials in Psoriasis

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	Induction: placebo or brodalumab 140 or 210 mg SC Q2W + week 1 (day 1 to week 10) [0.5 mL and 1 mL PFS]	661/633	Total: 266 weeks Primary analysis: 52 weeks	PASI75, sPGA BSA, PSSI, SSA, NAPSI, PROs	Subjects with stable moderate to severe plaque psoriasis for ≥ 6 months Biologic therapy candidate BSA involvement ≥ 10% PASI score ≥12 sPGA ≥ 3 Age 18 to 75 years
		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)	628/415			
		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)	149/106 36/35			
		Rescue (through week 52): brodalumab 210 mg SC Q2W	649 completed week 52 visit (558 subjects were ongoing at data cutoff of 12-MAR-2014			
		OLE: Brodalumab 140 or 210 mg SC Q2W (weeks 52 to 266 or inadequate response)				
20120103	Phase 3, multi-center, double-blind, randomized, active comparator- and placebo-controlled with induction, withdrawal, retreatment, rescue, and	Induction: placebo or brodalumab 140 or 210 mg SC Q2W + week 1 (day 1 to week 10) [0.5	1831/1776	Total: 266 weeks Primary analysis:	PASI75, sPGA BSA, PSSI, SSA, NAPSI, PROs	Subjects with stable moderate to severe plaque psoriasis for ≥ 6 months

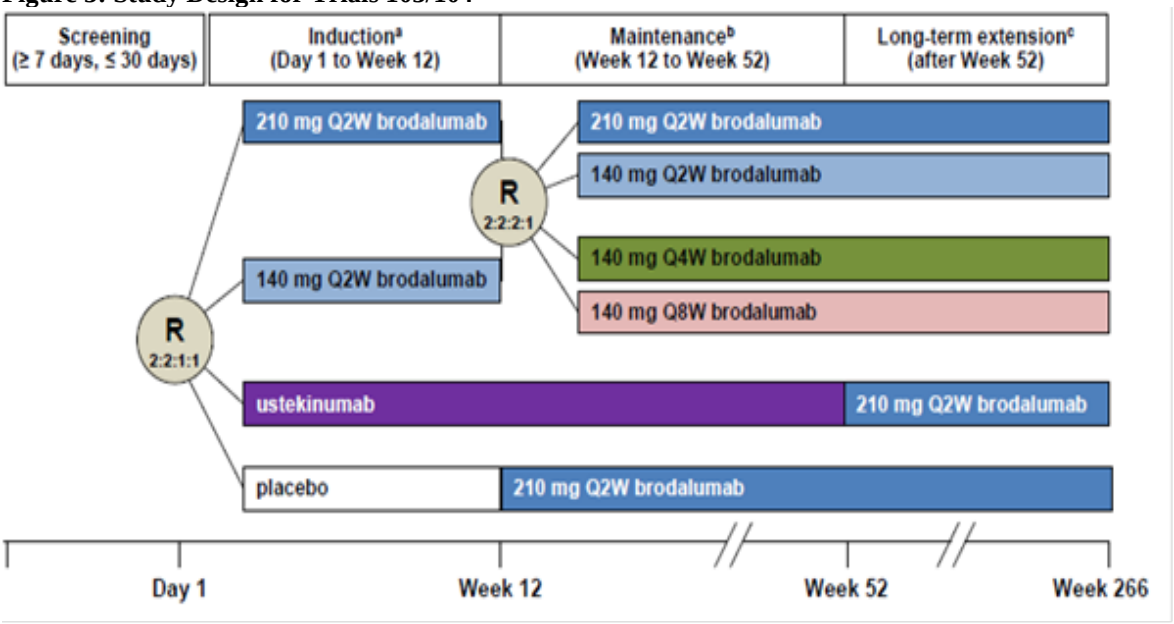
	open-label extension phases	mL and 1 mL PFS] or ustekinumab 45 or 90 mg SC (day 1 and week 4) Maintenance: brodalumab 140 mg SC Q2W, Q4W, or Q8W or brodalumab 210 mg SC Q2W (weeks 12 to 52 or inadequate response) or ustekinumab 45 or 90 mg SC Q12W (weeks 16 to 40 or inadequate response at week 16) Rescue: Brodalumab 210 mg SC Q2W or ustekinumab 45 or 90 mg SC Q12W OLE: Brodalumab 140 mg SC Q2W, Q4W, or Q8W or brodalumab 210 mg SC Q2W (weeks 52 to 266 or inadequate response) 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	1760/852 833/752 1601 completed week 52 visit (1533 subjects were ongoing at data cutoff of 22-SEPT-2014	52 weeks	cCSSRs, PHQ-8, safety and PK	Biologic therapy candidate BSA involvement ≥ 10% PASI score ≥12 sPGA ≥ 3 Age 18 to 75 years
20120104	Phase 3, multi-center, double-blind, randomized, active comparator- and placebo-controlled with induction, withdrawal, retreatment, rescue, and open-label extension phases	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) Maintenance: brodalumab 140 mg SC Q2W, Q4W,	1881/1816 1799/906	Total: 266 weeks Primary analysis: 52 weeks	PASI75, sPGA BSA, PSSI, SSA, NAPSI, PROs cCSSRs, PHQ-8, safety and PK	Subjects with stable moderate to severe plaque psoriasis for ≥ 6 months Biologic therapy candidate BSA involvement ≥ 10% PASI score ≥12 sPGA ≥ 3

		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) Rescue: Brodalumab 210 mg SC Q2W or ustekinumab 45 or 90 mg SC Q12W OLE: Brodalumab 140 mg SC Q2W, Q4W, or Q8W or brodalumab 210 mg SC Q2W (weeks 52 to 266 or inadequate response)	827/743 1656 completed week 52 visit (1597 subjects were ongoing at data cutoff of 30-AUG-2014			Age 18 to 75 years
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 photo/systemic psoriasis therapy Age 18 to 70 years

The integrated analyses of data are based primarily on the psoriasis trials from three Phase 3 placebo-controlled clinical trials (20120102, 20120103, and 20120104; hereon will be referred to as 02, 03, 04), of which 2 trials were also ustekinumab-controlled trials (Trials 03 and 04), and from 1 Phase 2 study (Study 20090062) and its open-label extension study (Study 20090403).

All 3 Phase 3 trials included a placebo-controlled 12-week induction phase, an open-label maintenance phase of 52 weeks duration, and an open-label long-term extension. The placebo-controlled Phase 2 study had a 12-week induction phase, and an open-label extension study. All clinical trials were terminated on May 22, 2015, at which time 3237 psoriasis subjects were in the study. Brodalumab was administered as subcutaneous (SC) injections of 210 mg every 2 weeks (Q2W), or 140 mg Q2W, every 4 weeks (Q4W) or every 8 weeks (Q8W) in the Phase 3 trials. In the single psoriasis Phase 2 study (20090062), brodalumab was administered at doses of 70 mg Q2W, 140 mg Q2W, 210 mg Q2W, and 280 mg Q4W.

Figure 3: Study Design for Trials 103/104



Note: Study 062 (Phase 2) and Study 102 (Phase 3) is not represented

The study design of the clinical trials allows for placebo comparison only through the 12-week induction phase; after Week 12 all subjects were switched to brodalumab. Trial subjects randomized to ustekinumab received it through Week 52 of the maintenance phase and were then switched to open-label brodalumab. The majority of subjects from all of the clinical trials were enrolled in the brodalumab long-term extension phase when the sponsor terminated the development program.

II. SUMMARY OF EFFICACY

A. Clinical Trial Data

The safety and 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 item score > 1) at Week 12. In Trials 03 and 04, for the comparison of brodalumab against ustekinumab at Week 12, the primary endpoint was PASI 100 (i.e., sequentially tested the brodalumab 210 mg vs. ustekinumab, then weight-based brodalumab vs. ustekinumab) with secondary endpoints of PASI 100 (brodalumab 140 mg vs. ustekinumab) and PASI 75 (weight-based brodalumab vs. ustekinumab).

For the comparison against placebo, both brodalumab doses were superior to placebo ($p<0.001$) for the co-primary as well as the secondary endpoints in each of the pivotal trials. For the comparison 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. Table 3 summarizes the efficacy results for the co-primary and the secondary endpoints for the three Phase 3 trials.

Table 3: Proportion of Subjects Achieving Treatment Success at Week 12 for Trials 02, 03, and 04 (ITT, NRI)

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

Source: reviewer table;

(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).

B. Efficacy Across Biologics for Psoriasis

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 αTNF and other cytokines in the inflammatory cascade have expanded the treatment options for the clinical management of psoriasis.

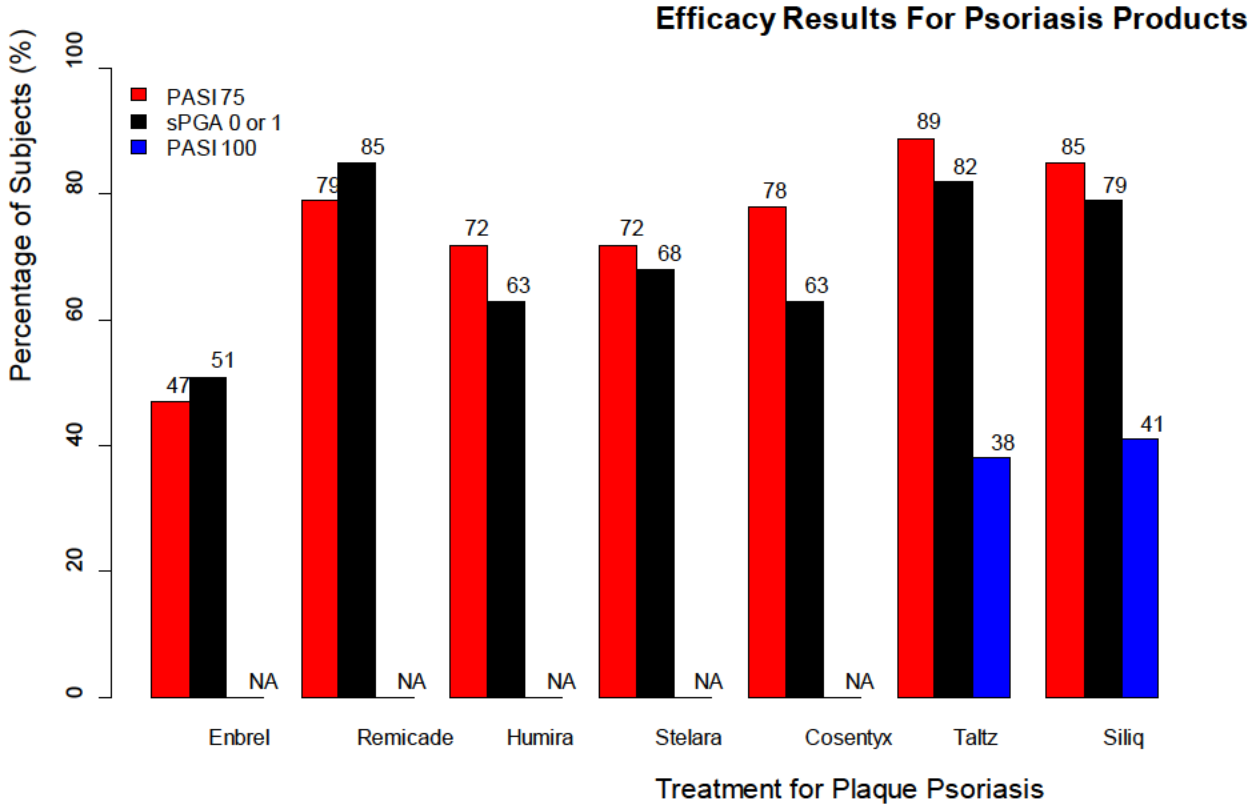
Table 4 and Figure 2 present descriptive comparisons of PASI 75, PGA, and PASI 100 response rates for the biologic products available on the U.S. market for treatment of moderate to severe adult psoriasis. Note that ixekizumab and secukinumab are IL17A antibodies directed at IL-17 cytokines. The mechanism of action for brodalumab is distinct in that it binds to certain IL-17 receptors rather than cytokines.

Table 4: 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%	85%	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 2: 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.

III. SUMMARY OF SAFETY

A. Clinical Trial Data

1. Deaths

In the Phase 3 clinical trials of psoriasis a total of 23 treatment-emergent fatal events were reported in brodalumab-treated subjects. 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. The other deaths included pulmonary embolism, aortic aneurysm rupture, and esophageal varices hemorrhage. 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.

a. Suicide Ideation and Behavior (SIB)

i. Introduction to 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 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.

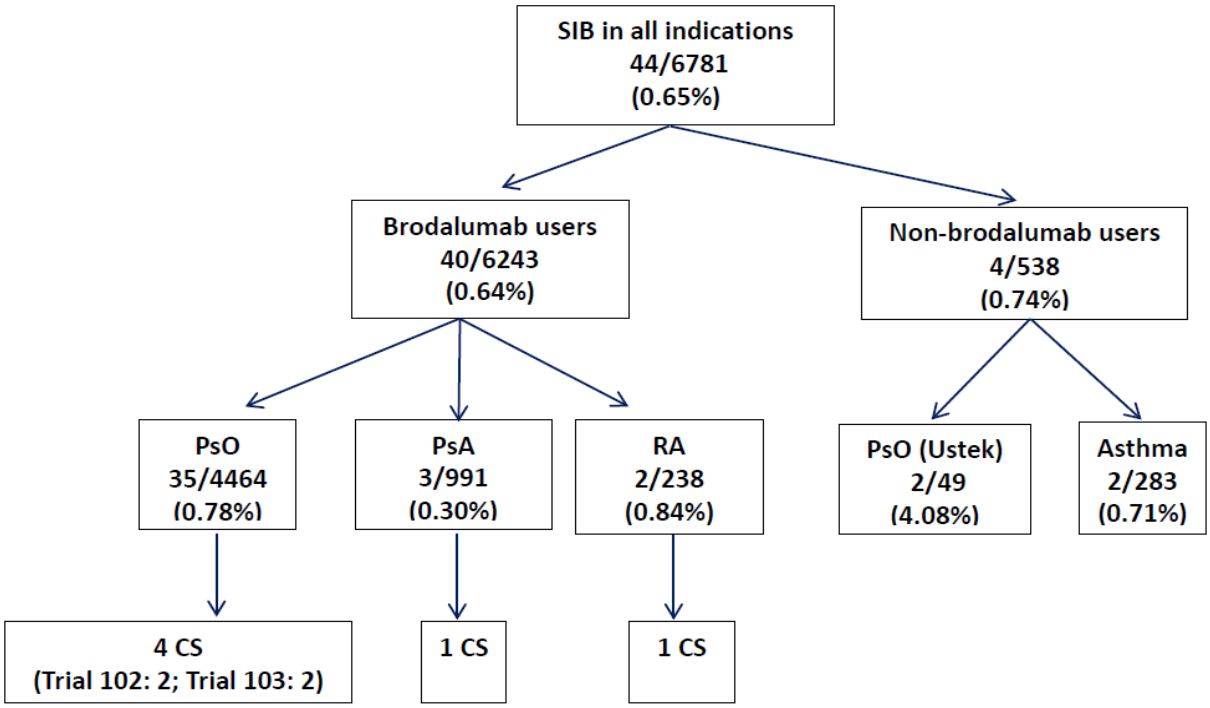
On May 13, 2015, after the initial pre-submission meeting, the Agency met with Amgen to discuss the safety signals of completed suicides and SIB observed in the clinical development program for brodalumab. A recommendation was made to the sponsor to further evaluate this risk and be prepared to comprehensively 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.

ii. Division of Biometrics 7 (DB7) Analysis of 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 3) 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 3: Distribution of suicidal ideation and behavior in brodalumab trials



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 5 summarizes selected baseline demographics and characteristics by original treatment assignment.

Table 5: Baseline demographics 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 6: 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 7 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 7: 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 8). 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 eC-

SSRS 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 8: 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 eC-SSRS was instituted more than mid-way through the Phase 3 clinical trials after discovery of the suicidality signal. Table 9 from the sponsor's submission, identified when the eC-SSRS was initiated and how many subjects received the assessment in each Phase 3 clinical trial.

Table 9: Study Week of first eC-SSRS 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 eC-SSRS assessment in the Phase 3 clinical trials, an evaluation of the severity of response can be weighed. Table 10 from the sponsor's submission, summarizes subjects on-study eC-SSRS responses through Week 52 and data cutoff. DB 7 is currently conducting a similar analysis.

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

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

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

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

The utility of the eC-SSRS and PHQ8 will be discussed in the consultative reviews.

iii. Division of Pharmacovigilance (DPV) Review of SIB and other Neuropsychiatric Events

- **Psoriasis and Psychiatric Morbidity**

Psychiatric and psychological factors play an important role in at least 30% of dermatological disorders[1]. 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[2]. 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 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[3]. 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[4].

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 life[1]. 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[2].

---

[1] 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

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

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

[4] 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.

- **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.

Table 12: Reported Psychiatric Events 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

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. 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 13: 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)

- **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 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.

- **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 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.

iv. Division of Epidemiology (DEPI) Review of SIB

In early 2014, the product sponsor identified suicidal ideation and behavior (SIB) as a safety concern in the brodalumab clinical trials, and implemented risk-mitigation strategies, including use of the electronic Columbia-Suicide Severity Rating Scale (eC-SSRS) and the Patient Health Questionnaire-8 (PHQ-8) to monitor subjects for depression and suicidality. Six brodalumab-treated subjects committed suicide. In May 2015, the product sponsor informed FDA they would be terminating all ongoing clinical trials across all indications.

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 a 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.[5] 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 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.

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

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.

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 found:

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.[6]

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 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;

[6] . 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

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.

v. Division of Psychiatry Products (DPP) Conclusions and Recommendations for SIB

See the Appendix for the complete review.

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 eC-SSRS.

One might also consider a possible beneficial effect on depression and anxiety based on the HADS finding in one placebo-controlled Study 02, 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 (i.e., 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.

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

b. Major Adverse Cardiovascular Events (MACE)

i. Introduction to MACE

Major Adverse Cardiac Events (MACE) is defined as CV death, myocardial infarction, or stroke in the application. 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.

A theoretical mechanism of action is antibodies affecting cytokine levels that are thought to have an effect on the inflammatory processes of cardiovascular disorders.[7] Brodalumab, an IL-17A receptor antagonist, block the effects of IL-17 at the receptor site, resulting in a compensatory increase in circulating IL-17[8]; the increase in IL-17A then impacts other cytokines in the cascade.[9] The theoretical effect is an acceleration of cardiovascular outcomes.

Evidence suggested that ustekinumab may have a positive risk for MACE; however, in the controlled trials with ustekinumab, there was 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.[10] Of note, briakinumab use (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 Agency and the European Medicines Agency (EMA) prior to completion of their reviews.[11]

ii. DB7 Analysis of MACE

MACE is defined as CV death, non-fatal myocardial infarction (MI), or non-fatal stroke that occurred after the first treatment dose and <42 days after the last treatment dose. As previously noted, MACE was adjudicated only in the Phase 3 PsO trials; therefore, the Phase 2 trials were

[7] 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.
[8] See Clinical Pharmacology section on IL17 affecting IL6
[9] Wang, Jie. Brodalumab treatment increased serum IL-17A concentrations in Study 20120102. Agency Clinical Pharmacology Review of Applicant Submission BLA 761032.
[10] MacCloskey, C. Review of Janssen's Report on "Analysis of MACE, Other Thrombotic Events and Other Cardiovacular Events in Ustekinumab Clinical Studies, PSOLAR and Postmarketing Data," August 25, 2014. FDA/OSE/OPE: 20-MAR-2015.
[11] Traczewski P and L Rudnicka. Briakinumab for the treatment of plaque psoriasis. Biodrugs 2012; 26(1):9 -20.

not included in this analysis. 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 21 summarizes subject baseline characteristics by original treatment arm.

Table 21: Baseline characteristics of the safety population in Phase 3 PsO 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

Analogous to the analysis of SIB, we analyzed MACE in the safety population by study phase; induction (first 12 weeks), active-control phase (first 52 weeks), and from randomization to end of follow-up. 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).

Table 22: Number (%) and follow-up time-adjusted incidence rates of adjudicated MACE in the active-controlled phase (first 52 weeks) of the three Phase 3 PsO trials

MACE	Brodalumab n = 3711	Brod 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)

†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 23: Number (%) and follow-up time-adjusted adjudicated MACE incidence rates in PsO trials from Day 1 to end of the follow-up

MACE	Brodalumab n = 3706	Brod 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

Table 24 summarizes the follow-up time-adjusted incidence rates of MACE by reported age and medical history in PsO 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 24: Number (%) and follow-up time-adjusted incidence of MACE by age and medical history in PsO trials from randomization to end of the 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

iii. DEPI Review of MACE

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. 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 1000 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

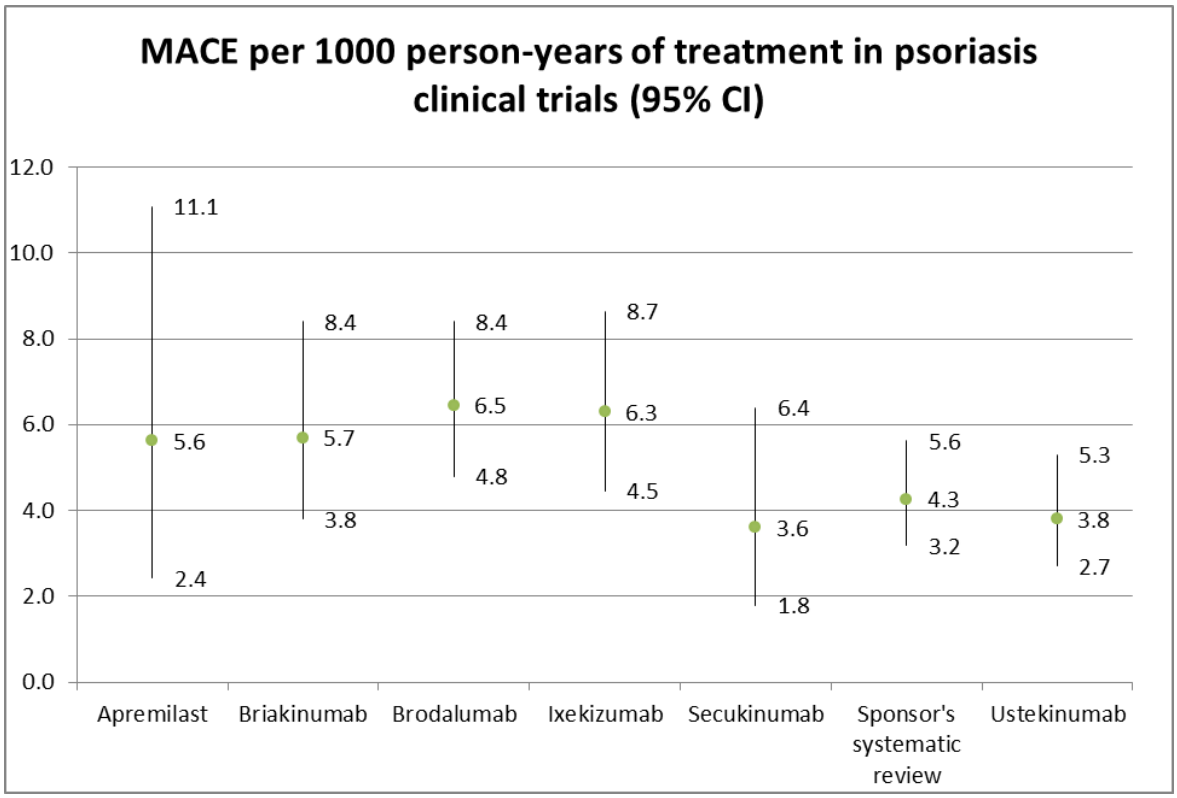
Summary data across products are subject to heterogeneity in patient characteristics, follow-up methods, & ascertainment of events. Data sources: (1) 4 mo su; (2) Langley et al. JEADV 2013, 27, 1252–1261; (3) 4 mo su; (4) MACE Information Request response; (5) MACE Information Request response

*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, briakumab and ixekizumab.



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.

iv. Division of Cardiorenal Products (DCRP) Review of MACE

See the Appendix for the complete review.

Summary

IL-7A 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
There was a paucity of reported events in the 12 week double blind period in this population considered to be at cardiovascular risk due to psoriasis. The MACE incidence rates beyond 12 weeks were low. The MACE data presented from the Phase 3 psoriasis clinical trials were inconclusive regarding the risk of MACE with brodalumab.

2. Serious Adverse Events (SAEs)

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).

Neutropenia, infections and infestations, and Crohn's disease will be discussed in detail in the Events of Special Interest. Table 26 illustrates the treatment-emergent serious adverse events experienced in the Phase 3 clinical trials.

Table 26: 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

	Brodalumab				
		Subjects With Brodalumab Exposure Only			
Preferred Term	210 mg Q2W after ustekinumab (subj-yr=715.2) (N= 567) 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 (Subj-yr=8655.0) (N= 4464) 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 stoke	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 (All)					
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.

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.

3. Common Adverse Events

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

Table 28: Common Adverse Drug Reactions during Induction Phase (12 weeks) – Integrated Safety Analysis Set – Psoriasis Subset

Adverse Reactions	Placebo (N=879) n (%)	Brodalumab		Ustekinumab (N=613) n (%)
		140 mg Q2W (N=1491) n (%)	210 mg Q2W (N=1496) n (%)	
Headache	31 (3.5)	81 (5.4)	64 (4.3)	23 (3.8)
Arthralgia	29 (3.3)	71 (4.8)	71 (4.7)	15 (2.4)
Fatigue	10 (1.1)	34 (2.3)	39 (2.6)	16 (2.6)
Oropharyngeal pain	10 (1.1)	32 (2.1)	31 (2.1)	8 (1.3)
Diarrhea	10 (1.1)	25 (1.7)	33 (2.2)	5 (0.8)
Nausea	10 (1.1)	26 (1.7)	28 (1.9)	6 (1.0)
Myalgia	3 (0.3)	20 (1.3)	26 (1.7)	4 (0.7)
Influenza	4 (0.5)	13 (0.9)	19 (1.3)	7 (1.1)
Injection site reactions (pain, erythema, bruising, hemorrhage, pruritus)	11 (1.3)	25 (1.7)	23 (1.5)	12 (2.0)
Neutropenia	4 (0.5)	11 (0.7)	15 (1.0)	5 (0.8)
Tinea infections (tinea pedis, versicolor, cruris)	2 (0.2)	4 (0.3)	15 (1.0)	3 (0.5)

Note that the most common AE were headaches and arthralgia. Most were mild and resolved. A dose-response relationship for common adverse events was not established as the AEs between the 140 mg Q2W dosing was similar to the 210 mg Q2W brodalumab dose.

4. Events of Special Interest

Suicidality and cardiovascular MACE have been identified as adverse events of special interest and were discussed in prior sections. Other events of interest include neutropenia, worsening of Crohn's disease, malignancies, and increased infections and will be described in this section.

Table 29: 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

	Maintenance Phase (52 weeks)		**Data cutoff date**	**First dose through 120-day safety update (end-of-study)**
Identified Risk	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)	700 (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.

a. 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 non-hematopoietic cells.

In the induction phase (12 weeks) of the clinical trials, incidence rates for AEs rates for 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 occurred in a placebo subject. 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 x 10^9/L to 0.5 x 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.

b. 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 30: Adverse Events in the Infections and Infestations SOC occurring ≥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 (brodalumab 210 mg Q2W constant dose), appendicitis (brodalumab 140 mg Q2W/210 mg Q2W group), sepsis (brodalumab 210 mg Q2W/140 mg Q2W/210 mg Q2W), cholecystitis infective (brodalumab 210 mg Q2W constant dose), and septic shock (brodalumab 210 mg Q2W).

Table 31: Adverse Events in Infections and Infestations SOC with Exposure-adjusted Rates ≥4 per 100 Subject-years For All Brodalumab Group (52 weeks) –Psoriasis subset

		Brodalumab					
		Variable Dose			Constant Dose		
Preferred Term	Ustekinumab (Subj-yr = 494.7) (N=613) n (r)	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.

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: Coccidiodomycosis in a 52-year old white male.

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

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 candidiasis led to discontinuation of investigational product and study in a 58 year old woman; 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.

c. Crohns' 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 excluded from brodalumab psoriasis clinical studies.

In the placebo-controlled phase of the clinical trials, only 1 subject in the placebo group had an 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 Crohn's disease on brodalumab 210 mg Q2W occurred in a 37 year-old white male on study day 209. This subject was discontinued from the study.

B. Clinical Pharmacology

1. PHARMACOKINETICS (PK) OF BRODALUMAB IN SUBJECTS WITH PSORIASIS

- *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 ($AUC_{0\text{-}day28}$)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 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.

2. Pharmacodynamics and potential role of IL-17A in suicidal ideation behavior (SIB)

- *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.

- *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).

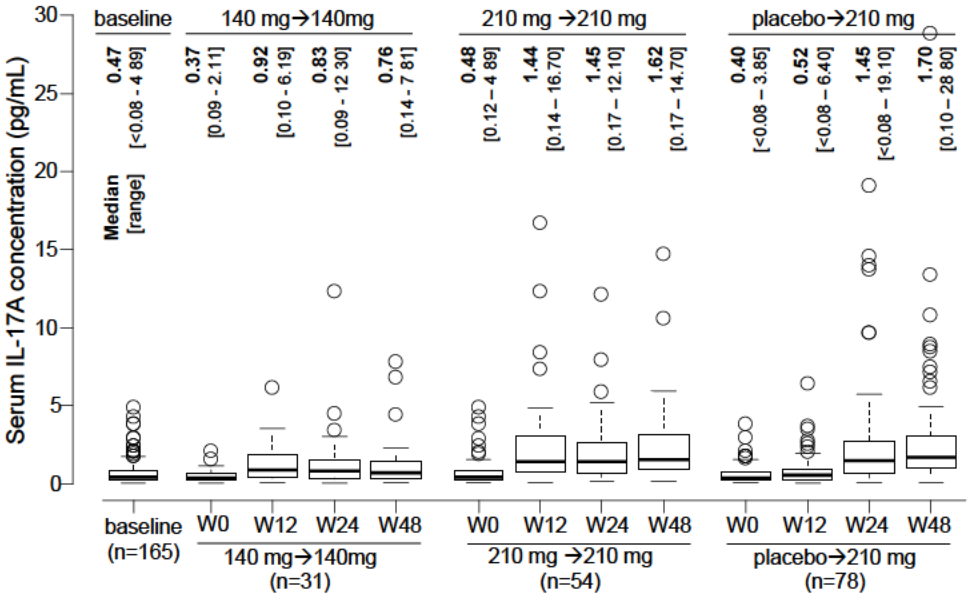


Figure B.2.a. Brodalumab increased serum IL-17A concentrations in subjects with psoriasis following 140 mg Q2W and 210 mg Q2W treatment. Pre-dose serum IL-17A concentrations were assessed at baseline, Week 12, Week 24 and Week 48 in a subgroup of subjects in Phase 3 Study 20120102. Placebo→210 mg treatment 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.*).

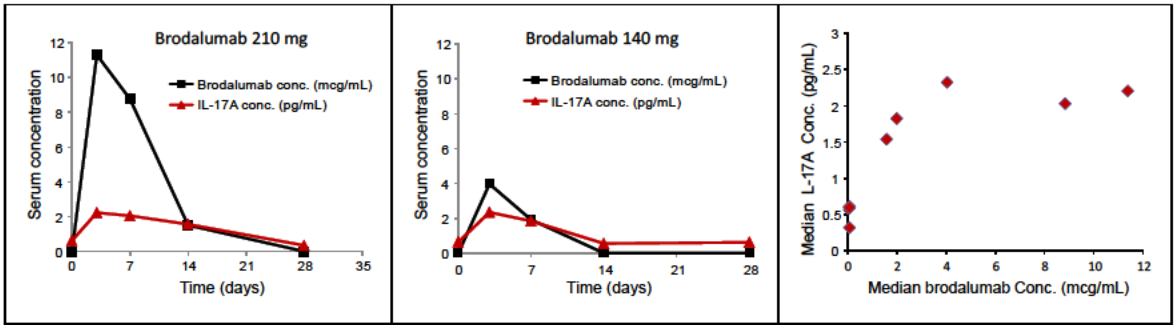


Figure B.2.b. Serum brodalumab and IL-17A concentrations in subjects with psoriasis following a single 140 mg and 210 mg treatment. Each time-point represents the median value based on 19-20 subjects in the 210 mg treatment group (left) and 9-10 subjects in the 140 mg treatment group (middle). Note the 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).

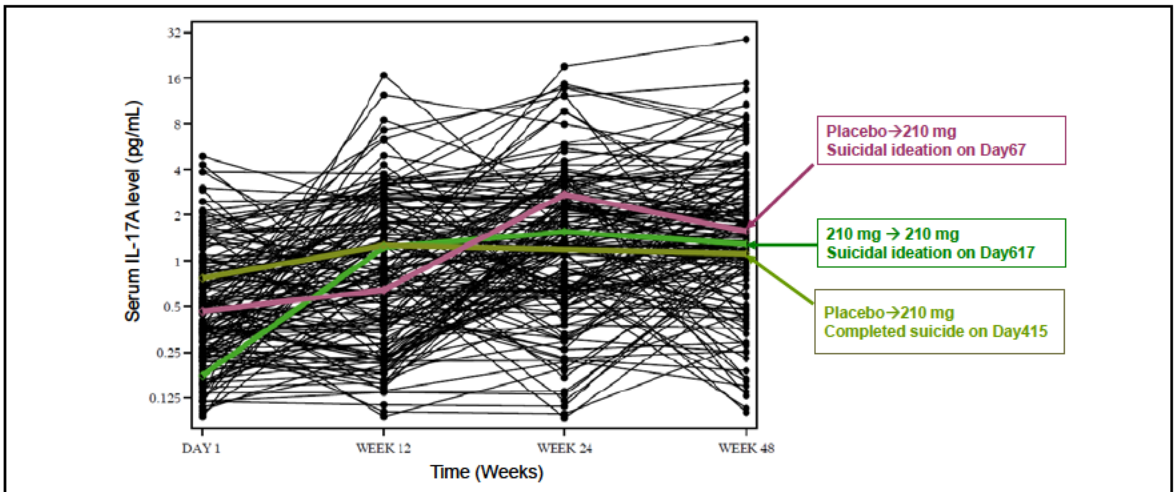


Figure B.2.c. Serum IL-17A levels in the three SIB subjects in Study 20120102. Pre-dose serum IL-17A concentrations were assessed at baseline, Week 12, Week 24 and Week 48 in a subgroup of subjects in Phase 3 Study 20120102. (*Data source: Reviewer's analysis and plot*).

- *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[12,13]. 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[14].
- 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[15].
- 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[16]. 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.

C. Risk Management

1. Risk Management Options for Suicidal Ideation and Behavior (SIB) Observed in Clinical Trials with Brodalumab

a. Introduction

This section summarizes the Division of Risk Management (DRISK) analysis of the benefits and limitations of risk management options for the risk of suicidal ideation and behavior (SIB) observed in clinical trials with Siliq (brodalumab). These options include labeling alone or labeling with one or more risk evaluation and mitigation strategy (REMS) elements. This

[12] 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.
[13] 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.
[14] 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.
[15] 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.
[16] 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.

memorandum does not cover all the known risks of brodalumab. See the Clinical Safety section of the FDA background materials for further information.

b. Background

i. Product Information

Brodalumab, an original biologic, is a human interleukin 17 Receptor A (IL-17RA) antagonist, with the proposed indication for the treatment of moderate to severe plaque psoriasis in adult patients who are candidates for systemic therapy or phototherapy. Blocking IL-17RA inhibits IL-17 cytokine-induced responses resulting in normalization of inflammation in the skin. To date, brodalumab has not been approved for any indication in any country. The proposed dose for brodalumab for the treatment of moderate to severe plaque psoriasis in adult patients[17] is 210 mg by subcutaneous injection at Weeks 0, 1, and 2 followed by 210 mg every 2 weeks. The product sponsor proposes to include a contraindication in patients with active Crohn's disease.

ii. Risk Evaluation and Mitigation Strategies[18]

The Food and Drug Administration Amendments Act (FDAAA), section 505-1 of the Food, Drug, and Cosmetic Act (FDCA) authorizes the FDA to require pharmaceutical sponsors to develop and comply with a REMS for a drug if FDA determines that a REMS is necessary to ensure that the benefits of the drug outweigh the risks. A REMS is a required risk management plan that uses risk minimization strategies beyond the professional labeling. In determining if a REMS should be required, FDA must consider the following factors:

(A) The estimated size of the population likely to use the drug involved.

(B) The seriousness of the disease or condition that is to be treated with the drug.

(C) The expected benefit of the drug with respect to such disease or condition.

(D) The expected or actual duration of treatment with the drug.

(E) The seriousness of any known or potential AEs that may be related to the drug and the background incidence of such events in the population likely to use the drug.

(F) Whether the drug is a new molecular entity.

The elements of a REMS can include: a Medication Guide (MG) or patient package insert (PPI), a communication plan (CP) to healthcare providers, elements to assure safe use (ETASU), and an implementation system. All REMS approved for drugs or biologics under

[17] Valeant Pharmaceuticals North America LLC. Proposed labeling for brodalumab (BLA 761032), submitted April 27, 2016 (eCTD Seq. No. 0022).
[18] FDA Draft Guidance for Industry – Format and Content of Proposed Risk Evaluation and Mitigation Strategies (REMS), REMS Assessments, and Proposed REMS Modifications, dated September 2009. Available at: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation /Guidances/UCM184128.pdf.

NDA and BLA must have a timetable for submission of assessments of the REMS. These assessments are prepared by the sponsor and reviewed by FDA.

ETASU can include one or more of the following requirements:

- Healthcare providers who prescribe the drug have particular training or experience or special certifications
- Pharmacies, practitioners, or healthcare settings that dispense the drug are specially certified
- The drug may be dispensed only in certain healthcare settings
- The drug may be dispensed to patients with evidence of safe-use conditions
- Each patient must be subject to monitoring
- Patients must be enrolled in a registry

Because ETASU can impose significant burdens on the healthcare system and reduce patient access to treatment, ETASU are required only if FDA determines that the product could be approved only if, or would be withdrawn unless, ETASU are required to mitigate a specific serious risk listed in the labeling. Accordingly, the statute [FDCA 505-1(f)(2)] specifies that ETASU:

- Must be commensurate with specific serious risk(s) listed in the labeling.
- Cannot be unduly burdensome on patient access to the drug.
- To minimize the burden on the healthcare delivery system, must, to the extent practicable, conform with REMS elements for other drugs with similar serious risks and be designed for compatibility with established distribution, procurement, and dispensing systems for drugs.

c. Benefit and Risk Considerations for Brodalumab

i. Summary of the Brodalumab Clinical Development Program[19]

The proposed indication for brodalumab is for the treatment of adult patients with moderate to severe plaque psoriasis who are candidates for systemic therapy or phototherapy. The product sponsor conducted three Phase 3 placebo-controlled studies (02, 03, and 04) with open-label, long-term extensions to support the efficacy of brodalumab for adult patients with moderate to severe plaque psoriasis who are candidates for systemic therapy or phototherapy. All three Phase 3 studies included a placebo-controlled 12-week induction phase, double-blind duration of 52 weeks, and an open-label long-term extension. Studies 03 and 04 used Stelara (ustekinumab) as an active comparator. Brodalumab was administered as subcutaneous (SC) injections of 210 mg every 2 weeks (Q2W), or 140 mg Q2W, every 4 weeks (Q4W) or every 8 weeks (Q8W) in the Phase 3 studies. All clinical trials were terminated on May 22, 2015, at which time 3237 psoriasis subjects were in the study.

[19] AstraZeneca. Clinical Overview for brodalumab, BLA 761032, submitted on November 16, 2016 (eCTD Seq. No. 0000)

ii. Key Findings of Brodalumab Efficacy Results

Brodalumab 210 mg and 140 mg were superior to placebo ($p<0.001$) in the treatment of moderate to severe plaque psoriasis in all Phase 3 trials for all co-primary and secondary endpoints (PASI 75, sPGA 0 or 1, PASI 100, PSI responder). When compared to ustekinumab, the 210 mg and the weight-based brodalumab doses were superior ($p<0.001$) for the primary endpoint (PASI 100). Brodalumab 140 mg was not superior to ustekinumab for the secondary endpoint of PASI 100 at Week 12 ($p=0.078$). Across all trials: 85% of patients achieved PASI 75 compared to 5% in placebo, 41% of patients achieved PASI 100, compared to 0.6% in placebo, and 41% achieved sPGA 0 compared to 0.6% in placebo. See the Clinical Efficacy section of the FDA background materials for further information on efficacy results.

iii. Serious Risk of Suicidal Ideation and Behavior (SIB) Seen With Brodalumab

The safety profile of brodalumab is based primarily on the integrated analyses of data from one double-blind, placebo-controlled Phase 2 psoriasis study (20090062), its open-label extension study (20090403), and the three Phase 3 psoriasis studies (02, 03, and 04). Additional supportive safety information for brodalumab is provided from the analyses of safety data from individual, unblinded Phase 2 studies in other indications including psoriatic arthritis, asthma, rheumatoid arthritis, and Crohn's disease. Adverse events of special interest observed in the clinical trials include infections, neutropenia, cardiac disorders (MACE events), malignancy, worsening of Crohn's Disease, and SIB. This review focuses on the serious risk of SIB. SIB is defined as a completed suicide, a suicide attempt, or a suicide behavior and suicide ideation.

Cumulatively through September 30, 2015, there were a total of 39 SIB events in 34 subjects, with 6 completed suicides (4 in the psoriasis program, one in the rheumatoid arthritis program, and one in the psoriatric arthritis program). There were 12 suicide attempts in 8 subjects; 6 suicidal behaviors in 6 subjects; and 20 suicidal ideations in 18 subjects.

Controlled clinical trials for the first 12 weeks of treatment were completed prior to identification of this potential signal and therefore it is unknown if a numerically disproportionate number of completed suicides would become statistically significant with continued use. Potential drug-related deaths by suicide may occur in the post-market setting without more information on the risk, association with the drug product, and how, if possible, to mitigate the risk.

iv. Risk Management Strategies Used in Clinical Trials

In March of 2013, FDA was informed of the first completed suicide reported in a patient taking brodalumab and in February 2014, SIB was identified as potential risk in the brodalumab program based on additional reports of SIB events in ongoing psoriasis Phase 3 studies. Due to these reports, risk mitigation activities were implemented globally across the program. The product sponsor used a variety of methods to identify at risk patients both prior to enrollment and during the study.

The product sponsor implemented a communication plan to alert investigators and patients of this potential risk. In February 2014, as part of this plan, the product sponsor sent a Dear Investigator Letter informing investigators of the risk of SIB. The following month, the Investigator's Brochure was also updated to include the risk.

In April 2014, consent forms were updated to inform patients of the risk of SIB. Protocol amendments were made for all new and ongoing brodalumab studies. The amendments included new criteria to identify at-risk subjects prior to enrollment and exclude them from study participation. Patient follow-up evaluations were added every 4 weeks to the schedule of assessments to assess SIB using the self-rated Electronic Columbia Suicide Severity Rating Scale (eC-SSRS tool) and to assess depression using the self-rated Patient Health Questionaire-8 (PHQ-8). Initially the brodalumab program did not include exclusion criteria for psychiatric and/or substance abuse comorbidities, including history of SIB. By the time the eC-SSRS and PHQ-8 were implemented, the majority of patients had completed the controlled, 52-week treatment period and switched to the open-label arm.

In May 2014, after protocol amendments were made, investigators received training on the tools and began actual implementation of the eC-SSRS and PHQ-8. Patients were discontinued from study drug and referred to a mental health care professional for further evaluation based on their scores on the eC-SSRS and PHQ-8. After implementation of the eC-SSRS and PHQ-8 assessment tools, the reported rate of suicidal behavior almost doubled (from 0.11 to 0.20 per 100 person years), and the reported rate of suicidal ideation increased10-fold (from 0.056 to 0.59 per 100 person-years), as expected. However, despite implementation of these tools, there was still one completed suicide that occurred post implementation. One year later, in May 2015, the product sponsor informed FDA they would be terminating all ongoing clinical trials across all indications.

These two self-rated scales may increase detection of SIB. However, it is unknown if the use of these two self-rated scales will have an impact on decreasing the risk of completed suicides.

d. Risk Management Proposed by the Product Sponsor

The product sponsor proposes specific labeling and a REMS to address the risk of SIB and exacerbation of Crohn's disease.

i. Product Sponsor Proposed Labeling

Labeling tools for brodalumab include the U.S. Prescribing Information (PI) for the prescribers, pharmacists and other healthcare professionals and a MG for the patient. The labeling for brodalumab proposed by the product sponsor, dated November 16, 2015, and updated most recently on April 27, 2016, includes a contraindication for patients with active Crohn's Disease. The proposed Warnings and Precautions section of brodalumab includes a use with caution in patients with history of Crohn's Disease and SIB, in addition to warnings for other serious adverse events (e.g., infections, tuberculosis, and vaccinations).

The proposed Warnings and Precautions section for SIB, which is the focus of this memo, instructs prescribers to evaluate all patients for signs of SIB and consider appropriate treatment

(e.g. referral to a mental health professional). The proposed label suggests weighing the potential risks and benefits before using brodalumab in patients with a history of depression and/or SIB. Under the proposed label, prescribers are advised to inform patients and caregivers to seek medical advice should signs of SIB, new onset or worsening depression, anxiety, or other mood changes emerge. Additionally, the proposed label advises prescribers to re-evaluate the benefits and risks of continuing treatment with brodalumab if such events occur.

ii. Product Sponsor Proposed REMS

The REMS proposed by the product sponsor was submitted on November 16, 2015, and amended February 4, 2016.

The goals of the proposed REMS are:

- to inform healthcare providers about the potential risk of SIB in patients with psoriasis, the need to counsel patients about the risks, and consideration of referral of patients to a mental health professional,
- to inform healthcare providers of the importance of proper patient selection; brodalumab is contraindicated in patients with active or a history of Crohn's Disease[20], and
- to educate patients to recognize the signs and symptoms of SIB, new onset or worsening depression, or other emerging mood changes, and to seek intervention should such signs emerge.

The product sponsor's proposed elements of the REMS include a MG and a CP targeted to healthcare providers (HCPs) who are likely to prescriber and/or inject brodalumab. The proposed CP includes the following: a Dear Health Care Professional Letter, a Dear Professional Society Letter, a HCP Fact Sheet, a Patient Wallet Card, a HCP Education Brochure, a REMS Coordinating Center, and REMS Website. The timetable for submission of assessment of the REMS is 18 months, 3 years, and 7 years from the date of the approval of the REMS.

e. DRISK Risk Management Considerations for Brodalumab

When considering the possible risk management strategies and determining the need for a REMS, a variety of factors are considered, as described in Section 2.2. The factors include but are not limited to available treatment options and any serious risks associated with those treatment options, the specific risks to be mitigated and the presence of any modifiable factors (e.g. the prevalence of SIB in the expected patient population and the practicality of modifying this behavior), as well as the clinical context of patient care.

[20] While the Applicant's proposed REMS includes goals to mitigate the risk of Crohn's disease exacerbation, DRISK believes that this can be handled through the Applicant's proposed labeled contraindication.

i. The Seriousness of Any Known or Potential Adverse Events Related to the Drug and Background Incidence of Such Events in the Population Likely to Use the Drug

SIB events were observed during clinical trials with brodalumab, including 6 completed suicides, in patients taking brodalumab. In the United States, there were 41,149 suicides in 2013 (a rate of 12.6 per 100,000 patient-years (PY)) and approximately 9.3 million adults (3.9% of the adult U.S. population) reported having suicidal thoughts in the past year.[21] Data from the National Vital Statistics System, from 1999-2014, shows suicide rates increased from 1999 through 2014 for both males and females for all ages 10-74. Based on available data the Division of Epidemiology-I (DEPI-I) calculated a rate of suicide in patients taking brodalumab (all indications) of 58 per 100,000 PY which is 3-4 times higher than in the rate of suicide in clinical trials of other biologics.[22]

Published literature points to an increased suicide risk in patients with psoriasis, atopic dermatitis, and acne, and a higher risk in patients whose skin condition is associated with clinically significant emotional distress, changes in body image, difficulties in close relationships, and impaired daily activities.[23] Some observational studies have also reported an increase in psychiatric disorders in patients with psoriasis.[24] However, specific comparative rates are not available. Other risk factors for suicide include a family history of suicide, previous suicide attempts, history of mental disorders, history of alcohol and substance abuse. [25]

While the product sponsor's proposed REMS includes goals and strategies to mitigate the risk of Crohn's disease exacerbation, DRISK believes that this can be handled through the product sponsor's proposed labeled contraindication. Therefore, at this time DRISK does not support including proper patient selection in patients' with active Crohn's Disease as a risk that requires a REMS to ensure the benefits outweigh the risks.

ii. The Size of the Population Likely to Use the Drug

Psoriasis is a multisystem autoimmune disease with predominantly skin and joint manifestations affecting approximately 2-3% of the U.S. population. Psoriasis can be mild, moderate, or severe. Approximately 7.5 million people in the United States have psoriasis. Approximately 80% of those affected with psoriasis have mild to moderate disease, with

---

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

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

[23] Picardi A, Lega I, Tarolla E. Suicide risk in skin disorders. Clin Dermatol. 2013 Jan-Feb;31(1):47-56.

[24] Cohen BE, Martires KJ, Ho RS. Psoriasis and the Risk of Depression in the US Population: National Health and Nutrition Examination Survey 2009-2012. JAMA Dermatol. 2016 Jan;152(1):73-9.

[25] Centers for Disease Control and Prevention. Suicide: Risk and Protective Factors. http://www.cdc.gov/violenceprevention/suicide/riskprotectivefactors html. Updated August 28, 2015. Accessed June 15, 2016.

20% having moderate to severe psoriasis affecting more than 5% of the body surface area.[26] Psoriasis patients with moderate to severe psoriasis can be treated with traditional systemic agents, phototherapy, or biologic agents, such as brodalumab.

iii. The Seriousness of the Disease or Condition

Moderate-to-severe psoriasis is a serious and, at times, disabling condition that has a substantial impact on patients' lives. The major manifestation of psoriasis is chronic inflammation of the skin. This may be characterized by disfiguring, scaling, painful, and erythematous, pruritic, plaques. The plaques may range from few to numerous covering a majority of the body's surface which may result in quality of life issues.[27] Quality of life of a patient may be affected by the burden of disease, and the severity and location of the skin lesions. There is currently no cure for psoriasis. Treatment focuses on managing symptoms, and the goal of treatment is to minimize or eliminate symptoms.

iv. The Expected Benefit of the Drug

The type of treatment for psoriasis depends on severity, the type, other medical conditions that the patient has, and how the patient reacted to previous psoriasis medications. The clinical benefit of brodalumab is similar to the newer IL-17A biologics (ixekizumab and secukinumab), with 85% of patients reaching PASI 75 (75% clearance of plaques) and 40% of patients achieving a PASI 100 (completely clear of plaques).

If approved, brodalumab may offer an alternative treatment option for adult patients with moderate to severe plaque psoriasis who are candidates for systemic therapy or phototherapy.

v. The Expected or Actual Duration of Treatment

Plaque psoriasis is a chronic disease that requires lifelong treatment. It is important to note that the risk window for SIB observed in the clinical trials with brodalumab appears to be unpredictable, occurring over a large and varying duration of exposure. Therefore at this time, it is unknown whether the risk of SIB increase, decreases, or remains the same over the treatment course.

vi. Whether the Drug is a New Molecular Entity

Brodalumab, a human interleukin 17 Receptor A (IL-17RA) antagonist, is a new biologic. Taltz (ixekizumab), approved in 2016, and Cosentyx (secukinumab), approved in 2015, are humanized IL-17A antagonists, also indicated for moderate-to-severe plaque psoriasis in adult patients who are candidates for systemic therapy or phototherapy. However, the mechanism of action of brodalumab differs from ixekizumab and seckunumab; brodalumab

[26] Menter A, Gottlieb A, Feldman SR, Van Voorhees AS et al. Guidelines of care for the management of psoriasis and psoriatic arthritis: Section 1. Overview of psoriasis and guidelines of care for the treatment of psoriasis with biologics. J Am Acad Dermatol 2008 May;58(5):826-50.

[27] Menter A, Gottlieb A, Feldman SR, Van Voorhees AS, Leonardi CL, Gordon KB,et al. Guidelines of care for the management of psoriasis and psoriatic arthritis: Section 1. Overview of psoriasis and guidelines of care for the treatment of psoriasis with biologics. J Am Acad Dermatol. 2008 May;58(5):826-50.

is an IL-17A *receptor* inhibitor whereas both ixekizumab and secukinumab are direct antagonists. It is unknown whether the difference in the mechanism of action of brodalumab has an impact on its safety profile. Brodalumab provides an alternative to the available biologic treatment options for adult patients with moderate to severe plaque psoriasis who are candidates for systemic therapy or phototherapy.

vii. Additional Risk Management Considerations for Brodalumab

In considering risk management options, it is important to clarify certain key aspects about the risks of SIB observed with brodalumab. The risk window for SIB observed in the clinical trials with brodalumab appears to be unpredictable, occurring over a large and varying duration of exposure. Although no specific predisposing factors have been identified for the SIB events, a preliminary subgroup analysis by the Division of Biometrics VII showed that brodalumab users with a history of depression and suicidality had higher SIB incidence rate than users without history. In addition, the limited duration of the placebo-controlled phase of the clinical trials did not provide sufficient exposure time to observe or compare SIB between brodalumab and the placebo arms. Although risk mitigation strategies may increase awareness and ensure knowledge about the risk of SIB, it is unknown whether risk mitigation strategies (as was employed in the clinical trials) can prevent SIB occurrence in an individual treated with brodalumab.

f. Risk Management Options for SIB Observed with Brodalumab

Regulatory options under consideration to mitigate the risks of SIB, if brodalumab is approved, include labeling alone or labeling with one or more REMS elements. Labeling and several REMS options are discussed below. A REMS would only be considered if optimized labeling (e.g., box warning) is not sufficient to ensure the benefits outweigh the risks of brodalumab.

i. Labeling

As mentioned above, labeling tools for brodalumab would include the U.S. Prescribing Information (PI) for the prescribers, pharmacists and other healthcare professionals and a MG for the patient. With labeling alone, the PI and MG will be used as the primary tools to communicate to prescribers and patients about the risks of SIB observed with brodalumab. The PI provides information for healthcare providers about the safe and effective use of drugs to assist them in deciding whether to prescribe brodalumab as well as to inform them of the importance of weighing the potential risks and benefits before using brodalumab in a patient with history of depression and/or SIB.

The brodalumab MG may provide information for patients about the risks seen with patients taking brodalumab and the importance recognizing the signs and symptoms of SIB.

Labeling strategies to address serious risks have included limiting the indication to second line therapy, including a limitation of use, a contraindication, inclusion of the risk as a warning (Section 5 of the PI) or in a a Boxed Warning. However, labeling alone may not be sufficient to mitigate the risk of SIB in this patient population. Prescribers of brodalumab, who will likely be dermatologists, may not be familiar with recognizing or treating SIB. In

addition, likely prescribers may not be aware of the tools that are used to screen for SIB or have experience with the use of these tools.

ii. Communication Plan

A REMS with a communication plan (CP) can be used to support implementation of an element of the REMS, and can also be used to inform healthcare providers involved in the care of patients taking the drug and professional organizations about risks of a drug and the practices for safe use.[28]

Recently approved CP REMS have included, but are not limited to, the following tools:

- REMS Letters for healthcare providers and Professional Societies that includes targeted concise' risk messaging
- Factsheet: Summary targeted for healthcare providers and addresses the specific risk(s) of concern that the REMS is addressing
- Journal Information Piece: Content would be similar to a factsheet
- Patient Wallet Card: Highlights risks and management of these risks for distribution by prescriber to patients.

A CP for brodalumab could inform HCPs by reinforcing certain information in the approved PI for brodalumab, (e.g. risks and/or specific safe use conditions of SIB).

Benefits of a CP REMS

- Targeted risk messaging distributed to HCPs to reinforce certain serious risks and safe use conditions described in prescribing information
- PI can be distributed with the CP materials
- May be more conducive to targeting a specialized prescribing population (i.e., dermatologists)

Limitations of a CP REMS

- Passive communication and will not ensure that every HCP receives and/or reviews the information.
- Not directed at patients, therefore will not ensure that patients will receive the risk messages

iii. Elements to Assure Safe Use (ETASU)

[28] FDA Guidance for Industry Format and Content of Proposed Risk Evaluation and Mitigation Strategies (REMS), REMS Assessments, and Proposed REMS Modifications Draft Guidance September 2009 http://www.fda.gov/downloads/Drugs/Guidances/UCM184128.pdf.

If it is determined that labeling and a REMS with a CP are not sufficient to ensure the benefits outweigh the risks, an ETASU may be required. ETASU are required medical interventions or other actions healthcare professionals need to execute prior to prescribing or dispensing the drug to the patient. Some actions may also be required in order for the patient to continue on treatment.

PRESCRIBER CERTIFICATION

Prescriber certification could include the following requirements:

- Prescribers are required to complete REMS training and/or enroll in the REMS program.
- Prescribers understand the need to, and agree to, provide counseling about SIB
- Prescribers agree to screen, and/or monitor patients for SIB

Benefits of Adding Prescriber Certification

- Provides additional assurance that, prior to prescribing brodalumab, prescribers have completed training and are aware of the need to counsel patients about the signs and symptoms of new or worsening SIB.
- Prescribers may be more informed about proper patient selection and the need to monitor patients receiving brodalumab.

Limitations of adding Prescriber Certification

- Screening of patients for SIB may decrease but will not eliminate the risk of suicide
- Patient access may be impacted if patients seeking treatment are challenged to find a prescriber certified in the REMS program.

PHARMACY CERTIFICATION

Pharmacy certification could be required in addition to a CP and prescriber certification. Pharmacy certification could include the following requirements:

- Pharmacists understand the need to, and agree to, distribute REMS-related educational information to patients that informs patients of the serious risks associated with brodalumab use.
- Pharmacists agree to fill prescriptions only from certified prescribers

Benefits of adding Pharmacy Certification

- Provides assurance that pharmacists are informed of the risks
- Provides greater assurance that brodalumab is only dispensed for prescriptions from certified prescribers
- Provides the opportunity for further patient counseling at the time of drug dispensation

Limitations of adding Pharmacy Certification

- Patient access may be impacted if pharmacy certification is required, patients can only

receive drug from a participating certified pharmacy.

DOCUMENTATION OF SAFE USE/MONITORING REQUIREMENT
Documentation of safe use conditions and/or a monitoring requirement could be required in addition to a CP, prescriber certification, and/or pharmacy certification. Documentation of safe use/monitoring could include the following requirements:

- Patient enrollment into the REMS with patient acknowledgement of the risk of SIB
- Required documentation of monitoring/screening of patients at pre-determined intervals for SIB

Benefits of Safe Use Conditions/Monitoring

- Ensures patients are fully informed prior to initiating therapy
- Requirement for continued patient assessment for SIB by the prescriber (analogous monitoring as was done in clinical trials)
- May detect SIB and potentially prevent suicide in some patients

Limitations of Safe Use Conditions/Monitoring

- Documentation of screening and monitoring requires enrollment of all patients into the REMS
- Will not eliminate the risk of suicide (It is unknown if the use of self-rated scales decreased the risk of SIB as these tools was implemented after the controlled segments of the clinical trials were completed).
- If required documentation of monitoring is linked to dispensing, could cause access and delays if documentation is not received in a timely manner

2. Discussion

In considering risk management strategies for brodalumab, the benefit of treatment must be weighed carefully against the seriousness of the risks associated with use, including the risk of SIB. If approved, brodalumab has the potential to be used in a large number of patients in the U.S. and likely prescribed by a prescriber specialty that may not be familiar with screening for and diagnosing SIB.

As detailed above, there are several risk management options that provide progressive levels of assurance that prescribers, pharmacists, and patients have been educated and understand the safe use conditions when taking brodalumab. However, each option has both benefits and limitations.

Risk management strategies described above may not prevent the risk of suicide in an individual treated with brodalumab. Tools may increase awareness and detection but cannot fully predict the act of committing suicide. The relationship between SIB and administration of

brodalumab is unpredictable, with events occurring across all timeframes after initiating treatment.[29]

Given the above discussion, even the most restrictive REMS may be limited in effectively mitigating the risk of SIB in the postmarketing setting, should brodalumab be approved.

3. Summary

This memorandum summarizes several options for risk management of the serious SIB events seen with brodalumab. Each option provides progressive levels of assurance that prescribers, pharmacists, and patients have been educated and understands the safe use conditions when taking this drug. However, no risk management strategy will completely eliminate the risk of SIB seen with brodalumab.

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

IV. PRELIMINARY TOPICS FOR THE ADVISORY COMMITTEE

The Division is convening this meeting to solicit the Committee's comments on the following topics. Please note, however, that these are preliminary topics and are still subject to change.

1. **Do the safety data for brodalumab suggest a signal for SIB?**

2. **Do the safety data for brodalumab suggest a signal for MACE?**

3. **Considering potential risks and benefits, do the available data support approval of brodalumab for the treatment of moderate to severe plaque psoriasis in adult patients who are candidates for systemic therapy or phototherapy?**

4. **If the overall benefit/risk profile for brodalumab is acceptable to support approval, comment on whether brodalumab should be approved with product labeling (including a Medication Guide for patients) to communicate safety risks.**

    a. Do you believe that a Boxed Warning is necessary to adequately convey the risks of SIB and MACE?

5. **Should brodalumab be approved as a second line treatment for moderate to severe plaque psoriasis given its safety profile?**

6. **Is a REMS necessary to ensure the benefits of brodalumab outweigh the risk of SIB?**

    a. If yes, what interventions or tools do you believe would help mitigate the risk of SIB?

7. **Please comment on pre-marketing or 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, cardiovascular events, and malignancy risk.**

APPENDICES

Appendix I

Division of Psychiatry Products Review

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

Table 15: 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-SSRS[30] and PHQ-8[31] 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.

[30] 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.

[31] 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.

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 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 16: 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 17: 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.

Table18: 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 1911: 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 20: Suicidal adverse events in brodalumab psoriasis trials before and after eCSSRS implementation (from sponsor)

Event	Pre eC-SSRS N=4464 Pyrs 5383.3		Post eC-SSRS N=3823 Pyrs 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

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.

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.

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.

Appendix II

Division of Cardiorenal Products (DCRP) Review of MACE

Executive Summary Assessment

Brodalumab is an interleukin-17A (IL-17A) receptor antagonist that was developed by Astra-Zeneca for the treatment of psoriasis. Brodalumab-mediated receptor antagonism resulted in an increase in serum IL-17A. This interleukin has been implicated in cardiovascular disease due to its pro-inflammatory action. DDDP consulted DCRP to assist in determining the risk of brodalumab-mediated MACE. There will be an Advisory Committee meeting July 19, 2016 to evaluate the benefit / risk of brodalumab for the treatment of psoriasis. The benefit of effective therapy for the treatment of will be compared to the risk of suicide ideation and the possibility of MACE that emerged from the data supporting the BLA.

There was a paucity of reported events in the 12 week double blind period in this population considered to be at cardiovascular risk due to psoriasis. The MACE incidence rates beyond 12 weeks were low. The MACE data presented from the phase-3 psoriasis clinical trials were inconclusive regarding the risk of MACE with brodalumab.

Background

Astra-Zeneca submitted a BLA for brodalumab, an IgG IL-17A receptor inhibitor, for the treatment of moderate to severe plaque psoriasis. This NME 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 dosing in phase 3 studies included a 12 week induction period and a maintenance period up to 52 weeks. Subjects were followed-up for up to week 266 weeks after randomization.

There were several biologics approved for the treatment of psoriasis that interfere with the IL-17 cascade as shown in Figure 1. These agents, such as ustekinumab (IL-12/23p40 inhibitor approved in 2009) and secukinumab (IL-17A inhibitor approved in 2015), directly inhibit the target interleukin whereas brodalumab inhibits the receptor thus causing an increase in IL-17A as shown in Figure 2. In this figure, there is a trend towards increased IL-17A levels as the dosing weeks increase.

Figure 4. Mechanism of Action of various monoclonal antibodies against the IL-17 family

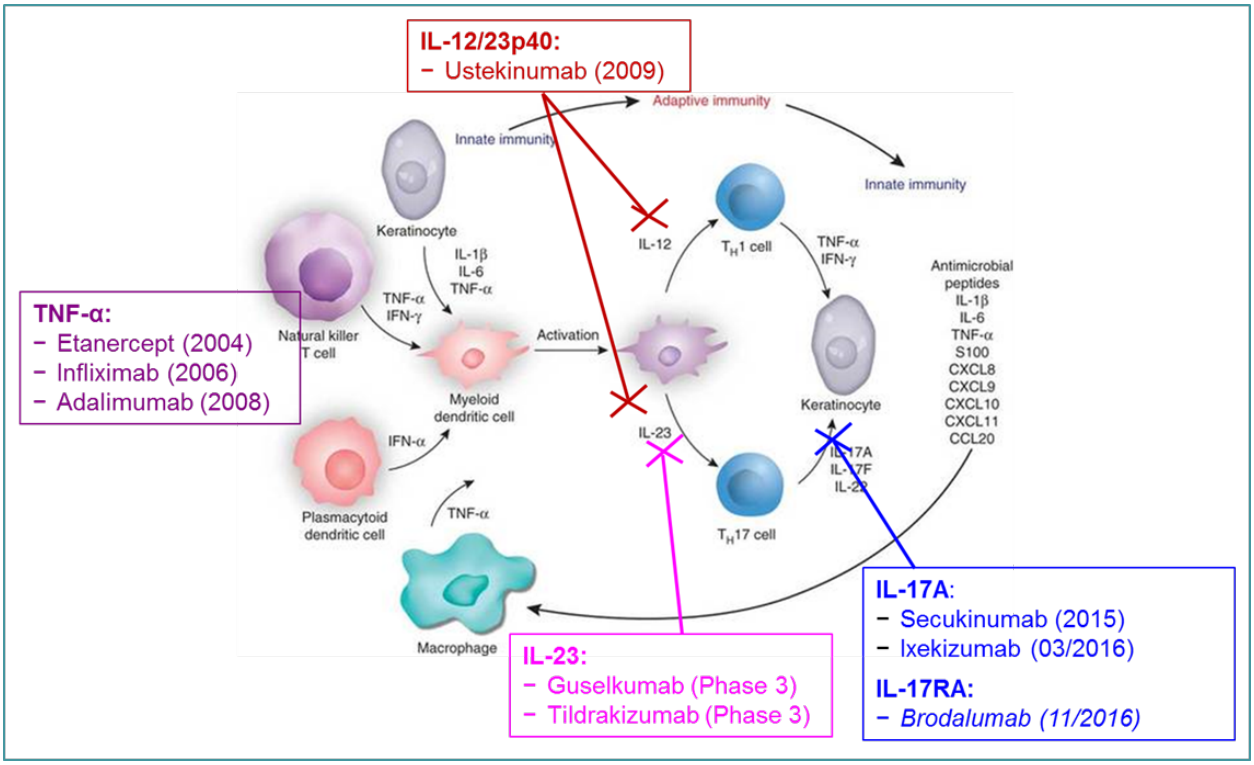
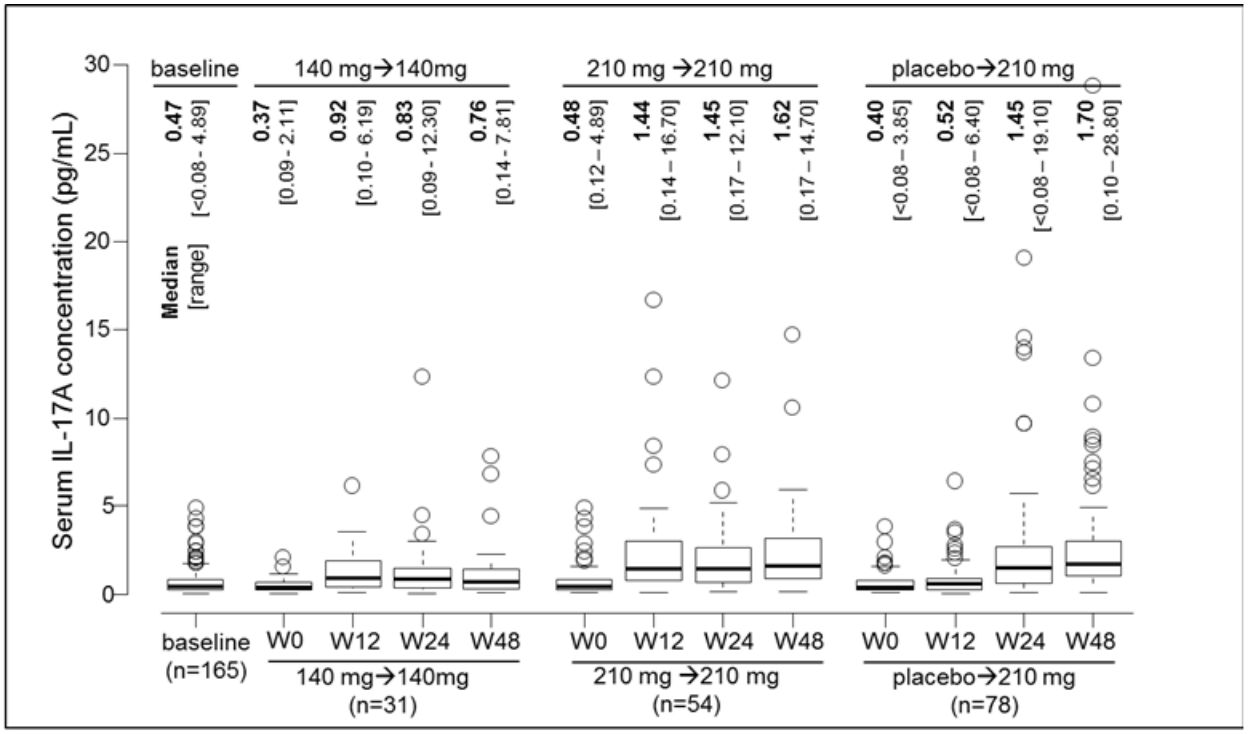


Figure adopted and reconstructed from literature Nature Biotech, 2011(29): 614-625.

Figure 5. Serum IL-17 concentration vs Brodalumab Dose



(*Data source: reviewer's plot*)

The Applicant expressed concern about the potential for IL-17A causing a detrimental effect on cardiac remodeling post myocardial infarction or post myocarditis (module 2.4, nonclinical overview-section 2.2.6.1). The Applicant's concern was hypothetical and not based on clinical data. Preclinical data reportedly ameliorated this hypothetical concern. In mouse models of myocardial infarction, inhibition of the IL-7 pathway resulted in improved survival, limited expansion of infarct, and prevention of left ventricular dilatation and systolic dysfunction. [32]

The role of IL-17 in the pathophysiology of psoriasis was evaluated with a focus on implications for therapy and cardiovascular co-morbidities.[33] Psoriasis is mediated by cross-talk between epidermal keratinocytes, dermal vascular cells and immunocytes, including activated antigen presenting cells (APCs), monocytes / macrophages, and TH1 and TH 17 cells. This leads to epidermal and vascular hyperplasia that is characteristic of lesional psoriatic skin. Pathology between psoriasis and cardiovascular disease is similar because of the involvement of key immunologic cell populations together with release of common inflammatory mediators such as IL-17A, thus suggesting a mechanistic link between the two diseases. Recent epidemiological evidence suggested that psoriasis patients have an increased risk of developing and dying from cardiovascular disease. Patients with ACS revealed significant increases in TH 17 cells and TH 17 cell-related cytokines (IL-17, IL-6, and IL-23), compared to patients with stable angina and

[32] Liao, YH, et al., 2012, Interleukin 17A contributes to myocardial ischemia/reperfusion injury by regulating cardiomyocytes apoptosis and neutrophil infiltration, Journal of American College of Cardiology, 59: 420-429
[33] Golden, J, et al., 2013, IL-17 in psoriasis: implications for therapy and cardiovascular co-morbidities, Cytokine, 62 (2): 195-201

normal subjects.[34] This suggested a potential role of IL-17 in coronary plaque destabilization and onset of ACS.

IL-17 is a cytokine with pleiotropic functions, where its role in various stages of atherosclerosis and its complications remains poorly understood. Studies suggested that IL-17 plays a dual role in atherosclerotic plaque stability and acute myocardial infarction,[35] thus awaiting direct studies for further understanding.

In the US, approximately 2% of the population is affected by psoriasis. Psoriasis can present at any age and has been reported at birth and in older people of advanced age. Psoriasis presents in a bimodal age distribution. The mean age of onset is 15 to 20 years. A second peak occurs at 55-60 years of age.[36]

In a REMS Oversight Committee presentation dated April 20, 2016 (slide 21), there were a total of 54 occurrences of MACE (defined in the 120 day safety update as CV death {12}, myocardial infarction {30}, and stroke {12}) in the brodalumab arms of phase 3 psoriasis trials from Day 1 to the end of study (8365.2 subject-years) compared to only 2 MACE occurrences in the comparator ustekinumab arm (1 CV death and 1 myocardial infarction in the same time period (511 subject-years).

The consulting division expressed concern about the MACE data reported in the safety update. Coupled with the hypothetical adverse effect of accumulating IL-17A, we were asked to help determine the risk to MACE with brodalumab.

The REMS Oversight Committee presentation of April 20, 2016 cited two key safety issues that emerged in the benefit-risk assessment: suicide ideation / suicide behavior and MACE. There will be an advisory committee meeting on July 19, 2016 to address the benefit and risk of brodalumab in the setting of other available agents for psoriasis.

Consultation Review

My consultation consisted of a review of the Applicant's clinical development plan and MACE data.

Clinical Development Plan

The development program for brodalumab is shown in Figure 3. A total of four indications were pursued: psoriasis, rheumatoid arthritis, asthma, and Crohn's disease.

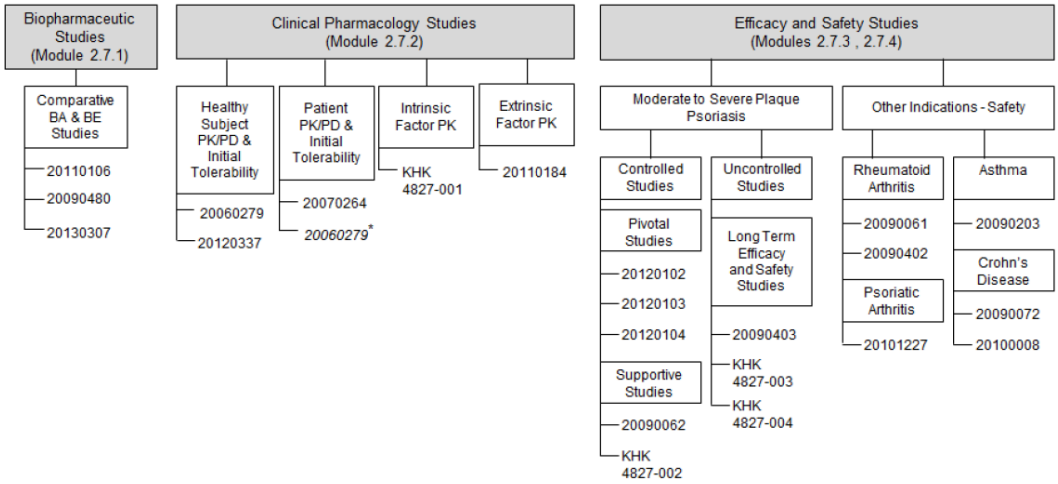
Three Phase 3 studies supported the BLA for the psoriasis indication (20120102, 20120103, and 20120104).

[34] Cheng, X, et al., 2008, the TH-17/Treg imbalance in patients with acute coronary syndrome, Clinical Immunology, 127, 89-97

[35] SU, S, et al., 2013, Interleukin-17 and acute coronary syndrome, Biomed and Biotechnology, 14 (8): 664-669

[36] Langley, R, et al., 2005, Psoriasis: epidemiology, clinical features, and quality of life, Annals of Rheumatic Diseases, 64 (Suppl II): ii18-ii23

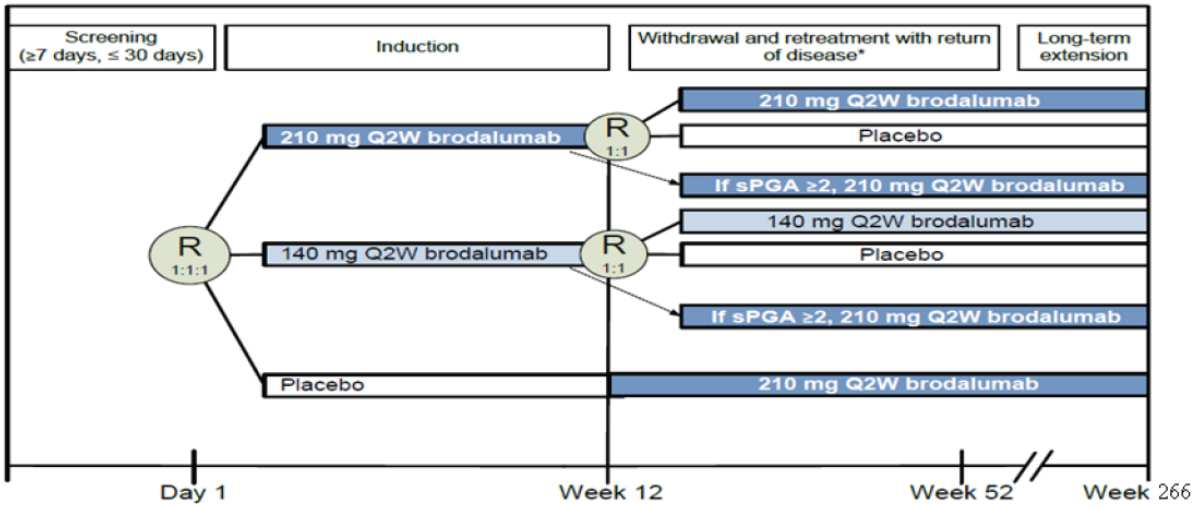
Figure 6. Overview of Brodalumab Development Program



Source: Applicant's BLA Module 2.5 Clinical Overview

The design of the phase 3 study 20120102 is shown in Figure 4. Subjects were randomized to one of three arms: brodalumab 210 mg q 2weeks, brodalumab 140 mg q 2 weeks, or placebo. Duration of treatment was 12 weeks. At the conclusion of 12 weeks, those subjects randomized to brodalumab 210 mg were re-randomized to the same dose or placebo. If any of these subjects had a static Physician's Global Assessment (sPGA) $\geq$ 2, they were maintained on brodalumab 210 mg q 2 weeks. Those subjects randomized to 140 mg q 2 weeks were similarly re-randomized at week 12 to continued treatment at that dose or placebo. If any of these subjects had a sPGA $\geq$ 2, they were placed on brodalumab 210 mg q 2 weeks. Treatment continued for 52 weeks followed by a long-term extension to week 266.

Figure 7. Study Design of 20120102 for psoriasis

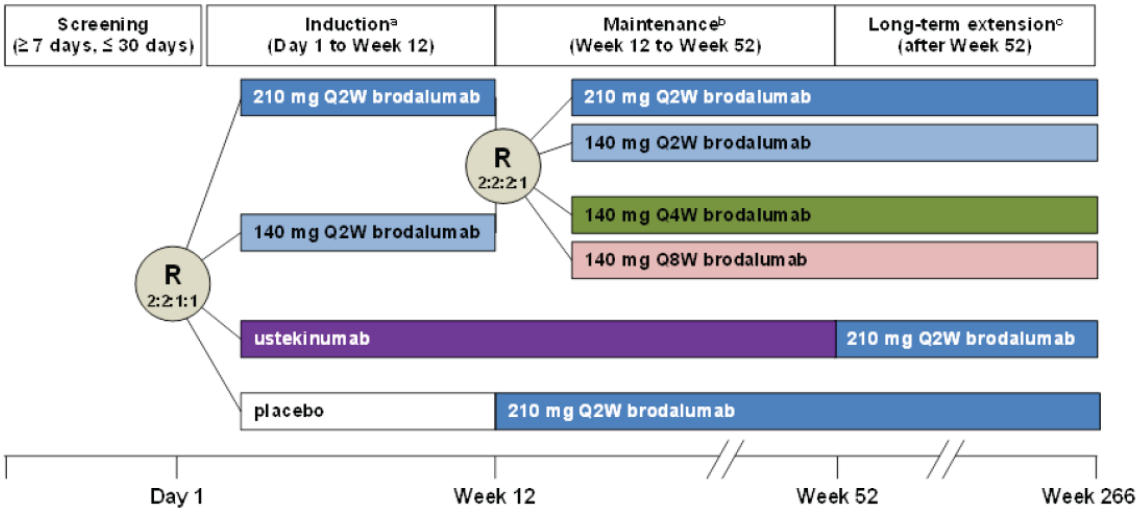


Source: Applicant's eCTD Module 2.5 Clinical Overview

The designs of phase 3 studies 20120103 and 20120104 are shown in Figure 5. In both these studies, subjects were randomized to one of four arms: brodalumab 210 mg q 2 weeks, brodalumab 140 mg q 2 weeks, ustekinumab (presumably at the prescribed dose of 45 mg initially, 45 mg at 4 weeks, and then 45 mg every 12 weeks for subjects weighing < 100 kg, and double the doses at all-time points for subjects weighing ≥ 100 kg), or placebo. The subjects randomized to the brodalumab arms were re-randomized at week 12 to one of 4 arms: brodalumab 210 mg q 2 weeks, brodalumab 140 mg q 2 weeks, brodalumab 140 mg q 4 weeks, or brodalumab 140 mg q 8 weeks. This treatment continued until week 266. Subjects randomized to ustekinumab were placed on brodalumab 210 mg q 2 weeks at week 52, and continued until week 266. Subjects randomized to placebo were placed on brodalumab 210 mg q 2 weeks at week 12 and continued until week 266.

The first 12 weeks of all three trials were double-blind. From week 12 to the end-of-study, the trials were open label.

Figure 8. Study Designs of 20120103 and 20120104 for psoriasis



Source: Applicant's eCTD Module 2.5 Clinical Overview

MACE occurrences were reported to be adjudicated by a Cardiovascular Events Committee (CEC) as mentioned in the applicant's summary of clinical safety (module 2.7.4). The Applicant stated that the CEC charter was located in appendix 16.1.13.5 of clinical study report 20120102. However, the CEC Charter was not found. This location provided the Safety or Data Monitoring Committee charter. The Safety or Data Monitoring Committee member list is shown in Figure 6 and the data flow process is shown in Figure 7. There were no cardiologists on the Safety or Data Monitoring Committee, but the charter mentioned the CEC and illustrated it as shown in Figure 7. I could not locate the CEC charter anywhere else in the submission. The data flow process suggested that MACE was adjudicated by the CEC before it was sent to the Safety or Data Monitoring Committee.

Figure 9. List of Monitoring Committee membership

List of DMC members:

DMC Chair:

Sterling West MD
Professor of Medicine
Department of Internal Medicine
University of Colorado Denver School of Medicine

DMC Statistician:

Ajit Tamhane PhD
Senior Associate Dean
Northwestern University
McCormick School of Engineering & Applied Science

DMC Member:

Ronald Simon MD
Head, Division of Allergy, Asthma, and Immunology,
Scripps Clinic, La Jolla, CA
Role on DMC: Physician

DMC Member:

Lawrence Eichenfield MD
Professor
Departments of Pediatrics and Medicine (Dermatology)
University of California, San Diego, School of Medicine
Role on DMC: Physician

DMC Member:

Anthony Ormerod MB, ChB, MRCP(UK), FRCP (Edin), MD (Abdn). FRCP (Lond)
Reader in Medicine and Therapeutics (Dermatology) ,
University of Aberdeen and Hon Consultant Dermatologist (NHS Grampian)
Role on DMC: Physician

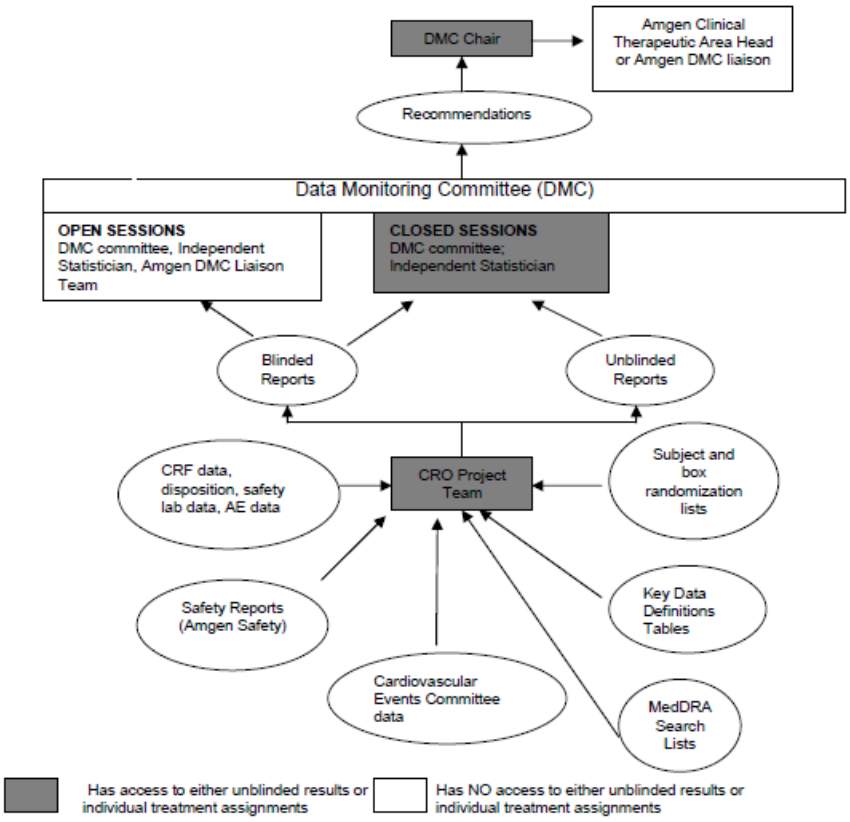
Source: Applicant's CSR from study 20120102, appendix 16.1.13.5

Figure 10. Interrelationships and data flow for the DMC

Brodalumab (AMG 827) Psoriasis Program
Data Monitoring Committee Charter
Version 3.0 Dated: 05 March 2013 Page 27

14. APPENDICES

14.1 Interrelationships and Data flow for the DMC



Source: Applicant's CSR to study 20120102, appendix 16.1.13.5

Data Review

Baseline demographics for studies 20120102, 20120103 and 20120104 are shown in Figure 8, Figure 9, and Figure 10 respectively. The majority of subjects were white males with a mean age 45 years (range 18 years-75 years). The majority of subjects were under age 65 years.

Figure 11. Baseline Demographics: Brodalumab studies 20120102, 20120103 and 20120104

	Placebo (N = 844)	Brodalumab 140 mg Q2W (N = 1458)	Brodalumab 210 mg Q2W (N = 1458)	Brodalumab All (N = 2916)	Total (N = 3760)	Weight-Based (N = 1460)
Sex - n (%)						
Male	588 (69.7)	1012 (69.4)	1013 (69.5)	2025 (69.4)	2613 (69.5)	1019 (69.8)
Female	256 (30.3)	446 (30.6)	445 (30.5)	891 (30.6)	1147 (30.5)	441 (30.2)
Ethnicity - n (%)						
Hispanic or Latino	91 (10.8)	162 (11.1)	166 (11.4)	328 (11.2)	419 (11.1)	160 (11.0)
Not Hispanic or Latino	753 (89.2)	1296 (88.9)	1292 (88.6)	2588 (88.8)	3341 (88.9)	1300 (89.0)
Race - n (%)						
American Indian or Alaska Native	2 (0.2)	6 (0.4)	7 (0.5)	13 (0.4)	15 (0.4)	6 (0.4)
Asian	29 (3.4)	62 (4.3)	49 (3.4)	111 (3.8)	140 (3.7)	60 (4.1)
Black (or African American)	26 (3.1)	43 (2.9)	39 (2.7)	82 (2.8)	108 (2.9)	39 (2.7)
Multiple	1 (0.1)	2 (0.1)	7 (0.5)	9 (0.3)	10 (0.3)	3 (0.2)

Page 1 of 3

Source: Applicant's ISE (module 5.3.5.3)

Figure 12. Baseline Demographics: Brodalumab studies 20120102, 20120103 and 20120104

	Placebo (N = 844)	Brodalumab 140 mg Q2W (N = 1458)	Brodalumab 210 mg Q2W (N = 1458)	Brodalumab All (N = 2916)	Total (N = 3760)	Weight-Based (N = 1460)
Race - n (%) (Cont'd)						
Native Hawaiian or Other Pacific Islander	3 (0.4)	8 (0.5)	10 (0.7)	18 (0.6)	21 (0.6)	11 (0.8)
White	769 (91.1)	1322 (90.7)	1319 (90.5)	2641 (90.6)	3410 (90.7)	1326 (90.8)
Other	14 (1.7)	15 (1.0)	27 (1.9)	42 (1.4)	56 (1.5)	15 (1.0)
Age (Years)						
n	844	1458	1458	2916	3760	1460
Mean	44.7	44.8	45.1	45.0	44.9	44.9
SD	12.9	13.0	12.9	12.9	12.9	13.0
Median	44.5	45.0	46.0	45.0	45.0	45.0
Q1, Q3	34.0, 55.0	35.0, 55.0	35.0, 55.0	35.0, 55.0	35.0, 55.0	35.0, 55.0
Min, Max	18, 86	18, 75	18, 75	18, 75	18, 86	18, 75

Page 2 of 3

Source: Applicant's ISE (module 5.3.5.3)

Figure 13. Baseline Demographics: Brodalumab studies 20120102, 20120103 and 20120104

	Placebo (N = 844)	Brodalumab 140 mg Q2W (N = 1458)	Brodalumab 210 mg Q2W (N = 1458)	Brodalumab All (N = 2916)	Total (N = 3760)	Weight-Based (N = 1460)
Age Group - n (%)						
< 65 years	791 (93.7)	1360 (93.3)	1369 (93.9)	2729 (93.6)	3520 (93.6)	1361 (93.2)
≥ 65 years	53 (6.3)	98 (6.7)	89 (6.1)	187 (6.4)	240 (6.4)	99 (6.8)

Page 3 of 3

N=Number of subjects randomized
% = n/N *100
Weight-based = Subjects ≤ 100 kg (at baseline) randomized to 140 mg Q2W or > 100 kg (at baseline) randomized to 210 mg Q2W
Treatment groups are defined as planned treatment for the induction phase

Source: Applicant's ISE (module 5.3.5.3)

Exposure data is shown in Figure 11. The majority of subjects were exposed to brodalumab 210 mg for approximately ≥ 12-18 months. There were 4074 subjects exposed to at least one dose of brodalumab 210 mg. Of these, 1788 were exposed to this dose of brodalumab for ≥ 12 months and 2809 subjects were exposed to brodalumab (any dose) for ≥ 12 months. The Applicant remarked that given the accumulative exposure for subjects receiving the 210 mg q 2 week dose, there was a high probability that a subject would have been on this dose at the time of any given AE.

Figure 14. Duration of cumulative brodalumab exposure at 210 mg

	Total Brodalumab 210 mg Q2W Exposure (Subj-yr=3810.1) (N=4074)	**Total Brodalumab Exposure (Subj-yr=5002.2) (N=4074)**
Duration of cumulative exposure - n (%)		
≥1 dose	4074 (100.0)	4074 (100.0)
≥3 months	3508 (86.1)	3830 (94.0)
≥9 months	2764 (67.8)	3329 (81.7)
≥12 months	1788 (43.9)	2809 (68.9)
≥18 months	461 (11.3)	1027 (25.2)
≥24 months	68 (1.7)	164 (4.0)
≥36 months	36 (0.9)	143 (3.5)
≥48 months	21 (0.5)	108 (2.7)
Duration of cumulative exposure (months)		
n	4074	4074
Mean	11.22	14.73
SD	6.59	8.56
Median	11.12	13.93
Min, Max	0.0, 52.6	0.0, 52.7

Source: Applicant's Summary of Clinical Safety

Efficacy was measured by Psoriasis Area Severity Index (PASI). In all three Phase 3 studies, a higher percentage of subjects achieved the endpoint of PASI 75 at week 12 in both brodalumab 210 mg q 2 weeks (range 83%-86%) and 140 mg q 2 weeks (range 60% to 69%) compared to placebo (range 3% to 8%).

Reports of MACE, defined as the composite of cardiovascular death, myocardial infarction, and stroke, in the first 12 weeks of treatment in placebo controlled phase 3 trials, are shown in Table 1. Only 3 subjects experienced a MACE (2 with myocardial infarction, and 1 with stroke) in the lower dosage brodalumab arm.

Table 12. MACE in 3 Phase-3 placebo-controlled trials (12 weeks)

Type of MACE	Placebo (N=842) n (%)	Ustekinumab (N=613) n (%)	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: from REMS Oversight Committee Presentation April 20, 2016

Reports of MACE for a 52 week follow-up period ("all brodalumab": everyone randomized to brodalumab or switched to brodalumab from ustekinumab, n=4270) and for the entire follow-up period (up to week 266) ("all brodalumab" from 1st dose through the 120 day safety update end of study", n=4273) in the phase 3 trials are shown in Table 2. The data is presented as adjusted for exposure and adjusted for follow-up time and measured in subject-years. The second column of data cumulatively includes the first column of data. I was not able to review data for the distinct time-period from week 52 to the end of study. All MACE occurrences took place while the subjects were on drug. The data showed no change in the incidence rate per subject year for brodalumab between drug initiation to 52 weeks and between drug initiation to the end of follow-up time.

Table 13. MACE in Phase 3 trials at 52 weeks and at end of follow-up (up to week 266)

MACE event		**1st dose through 120-DSU end of study**
	All-brodalumab N=4270 n (r)	**All brodalumab N=4273 n (r)**
Exposure-adjusted	**Subj-yr= 4793**	**Subj-yr=7870.4**
All MACE events	27 (0.6)	40 (0.5)
CV death	2 (0.0)	5 (0.1)
Myocardial Infarction	18 (0.4)	25 (0.3)
Stroke	7 (0.1)	10 (0.1)
Follow-up adjusted	**Subj-yr=4908.7**	**Subj-yr=8365.2**
All MACE events	32 (0.7)	54 (0.6)[a]
CV death	4 (0.1)	12 (0.1)[a]
Myocardial Infarction	20 (0.4)	30 (0.4)[a]
Stroke	8 (0.2)[b]	12 (0.1)[b]

Source: table provided by DDDP in inter-division communication April 19, 2016.

Table 3 shows the follow-up-time adjusted incidence of adjudicated MACE in the 52 weeks of the three phase 3 psoriasis trials as analyzed by the FDA Division of Biometrics # 7 (DB7). There were 23 MACE occurrences in 3711 subjects in the combined brodalumab arms: two dose arms combined in one cohort (incidence rate 0.6%, 95%CI 0.38—0.90) and 1 MACE in 489 ustekinumab subjects. The follow-up-time adjusted incidence rate of MACE for all brodalumab subjects (either randomized to brodalumab or switched to brodalumab from ustekinumab at the 52 week time point) was 0.7 per 100 subject years compared to 0.2 per 100 subject years for ustekinumab subjects. The apparent 3.5-fold higher incident rate per 100 subject years suggested a possible signal but the results were impacted by the paucity of events with a wide confidence interval.

Table 14. MACE events at 52 weeks for the three phase 3 trials.

Number (%) and follow-up time adjusted incidence rates of adjudicated MACE in the active-controlled phase (first 52 weeks) of the three phase 3 PsO trials

MACE	Brodalumab n = 3711	Brod 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	
MI	16 (0.5)		1 (0.2)	
Stroke	5 (0.13)		0	
Total	**23 (0.6, 95%CI: 0.38 – 0.90)**			
Incidence Rates (per 100 subject-years)				
Follow-up time (IR)	0.7 (3297.2)	(75.5)	0.2 (494.8)	0
	0.7 (95%CI: 0.43 – 1.02)			
Time from last dose to MACE (day)				
Median (min, max)	1.5 (-74, 24)		-34	
Time from first dose to MACE (day)				
Median (min, max)	207 (27, 357)		182	

Note: †One subject (20120103-10366037013) was originally in the placebo arm and was excluded from this analysis because MACE occurred 84 days prior to first dose of brodalumab.

Source: DB7 Review Document

Table 4 shows the follow-up-time adjusted adjudicated MACE incidence rates in the psoriasis trials from Day 1 to the end of follow-up (up to week 266). There were 48 MACE in 4273 subjects in the brodalumab arm: either originally randomized or switched from ustekinumab at some point during the follow-up period (incidence rate 1.1%, 95%CI 0.83—1.49). There were 2 MACE (CV death and myocardial infarction) in 49 subjects on ustekinumab. The follow-up-time adjusted incidence rate of MACE in these 4723 brodalumab subjects was 0.6 per 100 subject-years, compared to 7.3 per 100 subject years for ustekinumab subjects. The high incidence rate for ustekinumab was possibly an artifact of the small sample size in this arm. There was no difference in the incidence rate of MACE between a 52-week exposure period and an end-of-follow-up exposure period.

Table 15. MACE events from Day 1 to end of follow-up

Number (%) and follow-up time adjusted adjudicated MACE incidence rates in PsO trials from Day 1 to end of the follow-up

MACE	Brodalumab n = 3706	Brod 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)	
MI	28 (0.8)	0	1 (2.0)	
Stroke	11 (0.3)	1 (0.2)	0	
Total	**48 (1.1, 95%CI: 0.83 – 1.49)**			
Incidence Rates (per 100 subject-years)				
Follow-up time (IR)	0.7 (7587.1)	0.3 (778.1)	7.3 (27.5)	
	0.6 (95%CI: 0.42 – 0.76)			
Time from last dose to MACE (day)				
Median (min, max)	-1 (-336, 24)	17	-10.5 (-34, 13)	
Time from first dose to MACE (day)				
Median (min, max)	351 (27, 827)	893	160.5 (139, 182)	

Note: †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 84 days 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 to ustekinumab arm because it occurred >42 days after the last dose of brodalumab

Source: DB7 Review Document

After 52 weeks, it appeared that the majority of the subjects originally randomized to ustekinumab (n=613) were switched to brodalumab (n=124 by week 52 and an additional 443 after week 53 to the end of follow-up). Thus, by the end of follow-up, there were 567 subjects listed as receiving brodalumab after having been treated with ustekinumab. There was a residual of 49 subjects remaining on ustekinumab at the end of follow-up.

The adjusted MACE incidence rates per 100 subject-years by baseline characteristics and medical history in psoriatic trials from Day 1 to the end of follow up are shown in Table 5. There was a 12-fold increase in the incidence of MACE in subjects $\geq$ 65 years of age compared to subjects less than 40 years of age. There was a 13-fold increase in the incidence of MACE in subjects with "unknown" suicidality compared to subjects who did not have suicidality. The category "unknown" was assigned to subjects who answered "yes" to the question of ever having a suicidal thought but "no" to having a suicidal thought while participating in the clinical trial. There was a 9-fold increase in the incidence of MACE in subjects with a medical history of ischemic cerebrovascular or ischemic heart disease. There was a 4.7-fold increase in the incidence of MACE in subjects who had a medical history of cardiac or vascular disorders by MedDRA compared to subjects who did not have this history.

Table 16. MACE by baseline characteristics and medical history from Day 1 to follow-up

Adjusted MACE incidence rates by baseline characteristics and medical history in PsO trials from Day 1 to end of the follow-up

Subgroups for MACE	No. of brodalumab users (subject-years) N = 4464	No. of MACE (%)	Incidence rate per 100 subject-years
Baseline characteristics			
Age (years)			
< 40	1559 (3070)	5 (0)	*0.16*
>= 65	275 (530)	10 (4)	*1.89*
40 - 64	2439 (4765)	33 (1)	0.69
Suicidality			
No	3647 (7746)	29 (1)	*0.37*
Unknown	507 (382)	18 (4)	*4.71*
Yes	119 (237)	1 (1)	0.42
Depression/suicidality (Unknown as No)			
No	3605 (7148)	40 (1)	0.56
Yes	668 (1217)	8 (1)	0.66
Depression/suicidality			
No	3200 (6841)	26 (1)	*0.38*
Unknown	405 (307)	14 (3)	*4.56*
Yes	668 (1217)	8 (1)	0.66
Depression/suicidality (Unknown as yes)			
No	3200 (6841)	26 (1)	*0.38*
Yes	1073 (1524)	22 (2)	*1.44*
Medical history			
Ischemic cerebrovascular conditions or ischemic heart disease			
No	4121 (8101)	37 (1)	*0.46*
Yes	152 (265)	11 (7)	*4.15*
Cardiac or vascular disorders by MedDRA			
No	2917 (5824)	16 (1)	*0.27*
Yes	1356 (2541)	32 (2)	*1.26*

Source: DB7 Review Document

Assessment

My review of the data led to the following assessment:

- The Applicant expressed a concern about potential cardiac adverse events antecedent to the start of the Phase 3 program, and established a cardiovascular endpoint committee as part of the phase 3 plan to evaluate and adjudicate MACE as part of the safety monitoring plan. This concern appeared to be hypothetical and not supported by preclinical data. I would be interested in knowing why the expense of a CEC was incurred for a hypothetical concern not supported by preclinical data. I am also interested in knowing the incidences of MACE in the other development programs (i.e. asthma, rheumatoid arthritis, Crohn's disease).
- The role of IL-17 in cardiovascular disease in various stages of atherosclerosis and its complications remains poorly understood. Studies suggested that IL-17 plays a dual role

in atherosclerotic plaque stability and acute myocardial infarction (SU, 2013), thus awaiting direct studies for further understanding.

- I did not appreciate brodalumab or IL-17 levels at the time of MACE in order to explore drug causality.
- There was a paucity of reported events in the 12 week double blind period in this population considered to be at cardiovascular risk due to psoriasis.
- The 3 events during the 12-week double blind period occurred in the lower dose of brodalumab where the sample size in each brodalumab dosing arm were the same. This raised a question about drug-causality.
- The conglomeration of brodalumab arms were based on different dosing frequencies, thereby complicating an adequate assessment of drug-causality.
- The subject population was relatively younger than that usually associated with cardiac risk. I cannot rule out a drug-mediated risk of MACE in a population at higher risk.
- I could not locate the cardiovascular endpoint committee charter and therefore do not know how MACE was adjudicated or who performed the adjudication

Conclusions

In my opinion, the MACE data presented from the phase-3 psoriasis clinical trials were inconclusive regarding the risk of MACE with brodalumab.