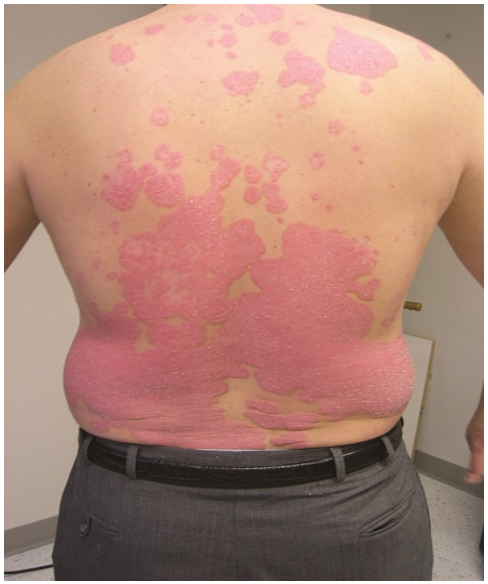
Dermatologic and Ophthalmic Drugs Advisory Committee Meeting

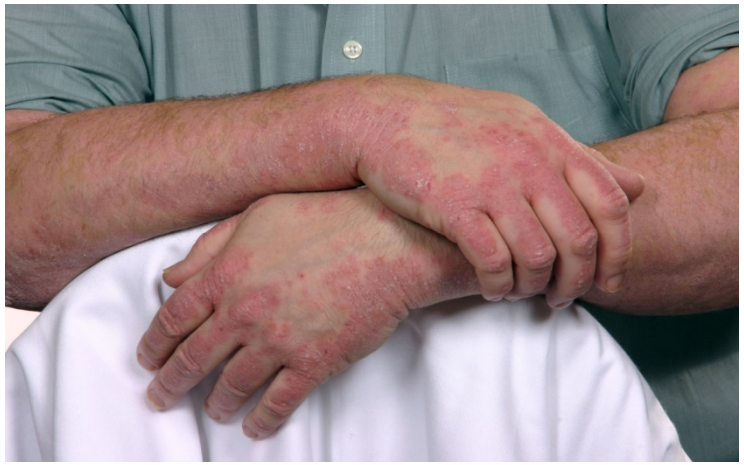
FDA Introductory Remarks

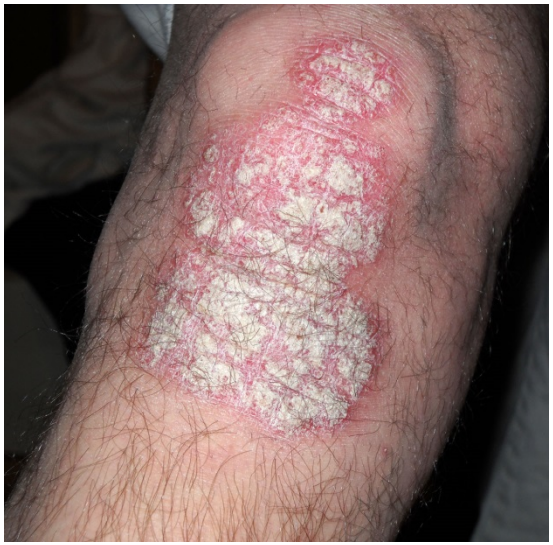
Kendall A. Marcus, MD
Director
Division of Dermatology and Dental Products
Office of Drug Evaluation III (ODE III)
Office of New Drugs (OND)
CDER, FDA

Plaque Psoriasis

- Psoriasis is a chronic, painful and frequently life-altering immune-mediated inflammatory skin disease associated with serious comorbidities







- Worldwide prevalence estimated at 2-3%
  - about 7.5 million affected in US

*Photos provided by the National Psoriasis Foundation

Current Treatment Options*

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	2008**	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

*Phototherapy and psoralen in combination with phototherapy are additional options
**Therapies not initially approved for psoriasis

SILIQ (brodalumab)
Product Description

- Original biologic
  - Human monoclonal immunoglobulin G2 (IgG2)
  - Binds to human **interleukin-17 receptor A** (IL-17RA)
- Proposed indication
  - Treatment of **adults** with moderate to severe plaque psoriasis who are candidates for systemic therapy or phototherapy

Specific Safety Issues

- **Infections**
- **Malignancy**
- **Neutropenia**
- **Worsening of Crohn's disease** (one subject discontinued due to new Crohn's onset)
- **Immunogenicity** (anti-brodalumab antibodies)
- ***Suicide Ideation and Behavior*** *(SIB)*
- **Cardiac disorders** (MACE)

Depression and Suicide Psoriasis Patients

- Various studies report higher rates of depression, anxiety and suicidal ideation in psoriasis patients
  - Severity of skin manifestations
  - Presence and severity of psoriatic arthritis
  - Disability/unemployment

- Psoriasis Patient-Focused Drug Development Meeting (March 2016)
  - Psoriasis impacts
    - Career choices and employment
    - Social contacts and intimacy
    - Reproductive choices
    - Fears of relapse

Suicidal Ideation and Behavior (SIB) Brodalumab Development Programs

- ***SIB***
  - suicide ideation
  - suicide behavior
  - suicide attempt
  - completed suicide

- 34 subjects had 39 SIB events
  - **6 completed suicides***
    - 4 in psoriasis program
    - 1 in psoriatic arthritis and 1 in rheumatoid arthritis programs

**One suicide adjudicated as indeterminate by investigator/wife*

Patient Profiles for Completed Suicides

Trial	Age/Sex (yr)	Race	Days from first dose brodalumab	Days from last dose brodalumab	History of depression
PsO*	56M	Asian	97	14	Y
PsO	39M	White	140	27	N
PsO	59M	White	329	58	N
PsO	56M	White	845	19	Y
PsA	57M	White	952	41	N
RA	42F	White	118	7	N

**Death by overdose adjudicated as indeterminate by investigator/wife*

Depression and SIB – Challenges in Ascertainment, Signal Detection and Cross-Study Comparisons

- Cultural/Personal
  - Cultural stigma
  - Population level incidence of suicide
  - Social/financial/medical considerations
- Ascertainment methods
  - Passive
  - Retrospective adjudication (C-CASA)
  - Active (PHQ, eC-SSRS, HADS)
- Development program
  - Initial versus supplemental indication
- Variability in enrollment criteria
  - Exclusion criteria for significant psychiatric illness/suicidality

Tools Implemented During Brodalumab Clinical Trials

- **Risk Communications**
  - Dear Investigator Letter
  - Updated Informed Consent Forms and Protocols
  - Updated Investigator's Brochure

- **Clinical Trial Revisions**
  - Incorporation of assessment tools
    - *Electronic Columbia Suicide Severity Rating Scale (eC-SSRS)*
    - *Patient Health Questionaire-8 (PHQ-8)*

Implementation of Self-Rating Scales

- **Patient Health Questionaire-8 (PHQ-8)**
  - Validated eight-item assessment tool
    - **Symptoms and signs of depression**
- **Electronic Columbia Suicide Severity Rating Scale (eC-SSRS)**
  - Validated instrument
    - **Severity and frequency of SIB**
  - 6-point numeric scale
    - no ideation (0)
    - active ideation with plan and intent (5)
  - *Retrospective assessment of lifetime and on-study SIB

- Referral to a mental health professional and/or discontinuation of investigational product based on scores

Data Analysis for SIB
Columbia-Classification Algorithm (C-CASA)

- Electronic text string search of databases for terms that may indicate SIB
- Constructed narratives of events reviewed and classified
- First used in review of clinical trial data for ***psychiatric*** indications in 2004
- Utilized in data analysis of the following biologics applications for psoriasis:
  - Apremilast (2014)
  - Secukinumab (2015)
  - Ixekizumab (2016)
  - Brodalumab*

*In addition to eC-SSRS

C-CASA Classification Scheme

Suicidal	1. Completed Suicide 2. Suicide Attempt 3. Preparatory Actions Towards Imminent Suicidal Behavior 4. Suicidal Ideation
Indeterminate	5. Self-injurious Behavior Intent Unknown 6. Not Enough Information: Death 9. Not Enough Information: Non-Death
Non-suicidal	7. Self-Injurious Behavior Without Suicidal Intent 8. Other (Accident; Psychiatric; Medical)

Source: Adapted from Posner K.: C-CASA and C-SSRS in CNS Clinical Trials Development and Implementation
http://www.nationalacademies.org/hmd/~/media/Files/Activity%20Files/Research/NeuroForum/Suicidality%20meeting/web%20files/Posner.pdf

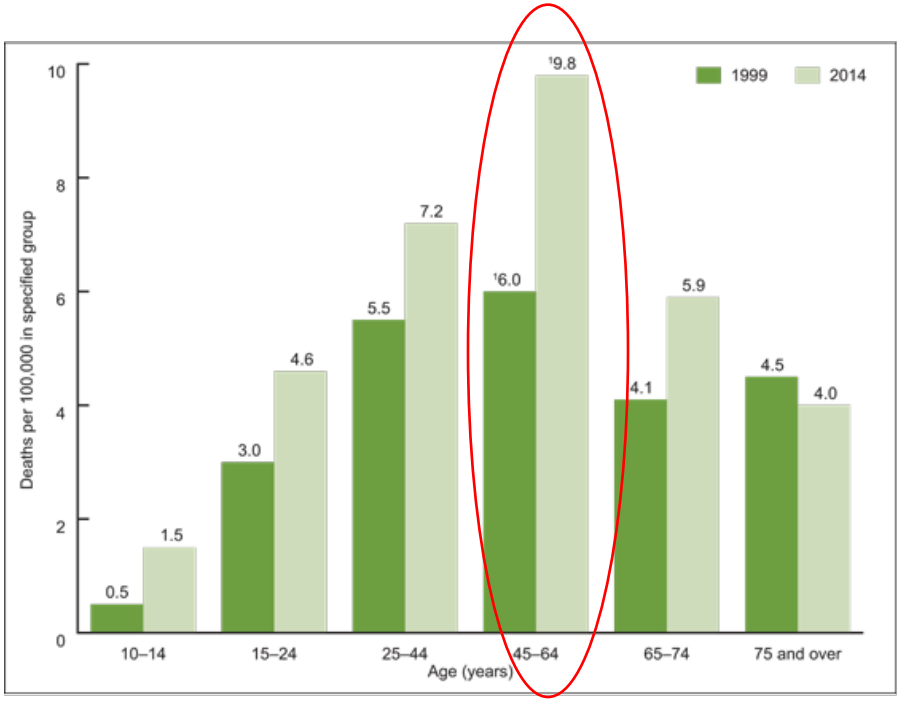
C-CASA
Why? A Few Examples

Unadjudicated Adverse Event Label	Narrative
Suicide attempt	Subject engaged in "automutilation" where she slapped herself in the face
Suicide attempt	Subject had thoughts of killing self but no intent to act on the thoughts
Abdominal hernia	Subject experienced eventration after a laparotomy due to an abdominal wound caused by self-inflicted gun shot.
Trauma	Subject attempted to stab himself in the abdomen which resulted only in minor injury. Investigator did not consider it a true suicide attempt.
Suicide attempt	Subject explained event of hitting head on the wall as "it is like my thoughts are about to explode".

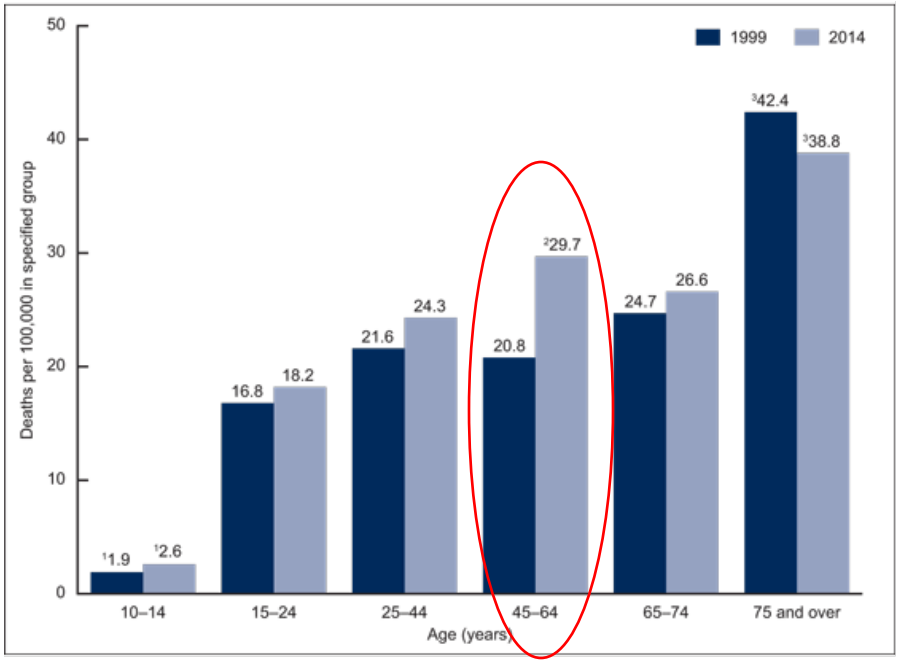
Source: Adapted from Posner K.: C-CASA and C-SSRS in CNS Clinical Trials Development and Implementation
http://www.nationalacademies.org/hmd/~/media/Files/Activity%20Files/Research/NeuroForum/Suicidality%20meeting/web%20files/Posner.pdf

CDC – National Vital Statistics
Suicide Rates in US (1999 to 2014)

Suicide rates for females, by age



Suicide rates for males, by age



Issues for Consideration

- Adequacy of the safety evaluation
  - Suicidal Ideation and Behavior (SIB)
  - Major Adverse Cardiovascular Events (MACE)
- Overall benefit/risk profile of brodalumab
  - Risk management
- Post-marketing studies/trials

Questions and Discussion

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

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

        i. Suicide Ideation and Behavior (SIB)?

        ii. Major Adverse Cardiovascular Events (MACE)?

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

Questions and Discussion

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

    a. Yes, with labeling alone to manage the risks

    b. Yes, but only if certain risk management options for SIB beyond labeling are implemented

    c. No

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

Questions and Discussion

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

Dermatologic and Ophthalmic Drugs Advisory Committee Meeting

SILIQ (brodalumab) for injection, for subcutaneous use for the treatment of moderate to severe plaque psoriasis

July 19, 2016

Efficacy and Safety of Brodalumab for Psoriasis

FDA Speakers

Gary Chiang, MD, MPH
Medical Officer
Division of Dermatology and Dental Products

Jean Kim, MD, MA
Medical Officer
Division of Psychiatry Products

Ling Lan, PhD
Biostatistics Reviewer
Division of Biostatistics VII

Robert L. Levin, MD
Director
Division of Pharmacovigilance-I (DPV-I)

Andrew Mosholder, MD, MPH
Medical Officer
Division of Epidemiology I (DEPI-I)

Jasminder Kumar, PharmD
Risk Management Analyst
Division of Risk Evaluation (DRISK)

Kendall A. Marcus, MD
Director
Division of Dermatology and Dental Products

Overview

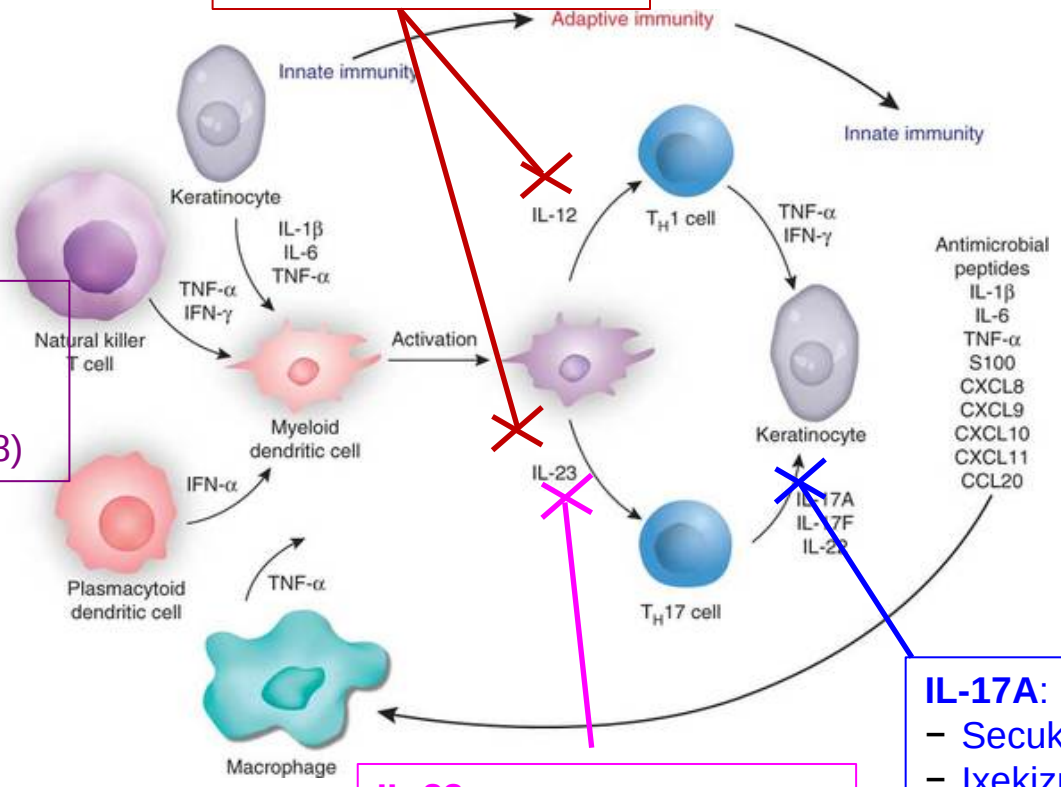
- Pharmacokinetics/Pharmacodynamics
- Efficacy
- Safety Assessment
  - Common/Serious Adverse Events/Events of Interest
  - Safety signals
    - Suicide Ideation and Behavior (SIB)
    - Major Adverse Cardiovascular Events (MACE)
- Risk Management Options
- Questions

Clinical Pharmacology

Gary Chiang, MD, MPH
Medical Officer
DDDP, ODE III, OND, CDER, FDA

Therapeutic Targets for Biologics in Psoriasis

IL-12/23p40:
- Ustekinumab (2009)



TNF-α:
- Etanercept (2004)
- Infliximab (2006)
- Adalimumab (2008)

IL-23:
- Guselkumab (Phase 3)
- Tildrakizumab (Phase 3)

IL-17A:
- Secukinumab (2015)
- Ixekizumab (2016)

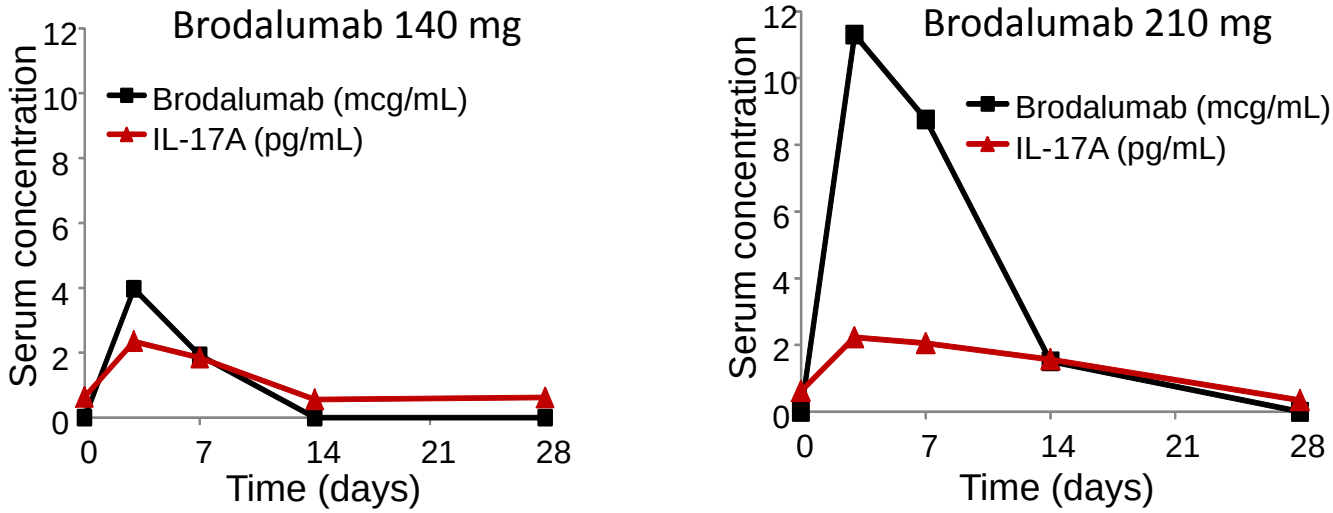
IL-17RA:
- *Brodalumab*

Pharmacokinetics of Brodalumab

- Nonlinear PK
  - Likely due to receptor/target-mediated drug disposition.
  - From 140 mg to 210 mg, the exposure (AUC) increased ~ 3-fold.
  - Brodalumab concentrations became undetectable at 32 days (140 mg Q2W) and 63 days (210 mg Q2W) after discontinuation.
- Intrinsic factors
  - Body weight: exposure decreases with increasing body weight
  - Age, sex, or race: no effect on brodalumab PK
- Extrinsic factor (drug-drug interaction)
  - Midazolam exposure increased by 24% when administered 7 days after a single 210 mg SC dose of brodalumab.

Pharmacodynamics of Brodalumab
- Serum IL-17A level increased after treatment

Single Dose Study

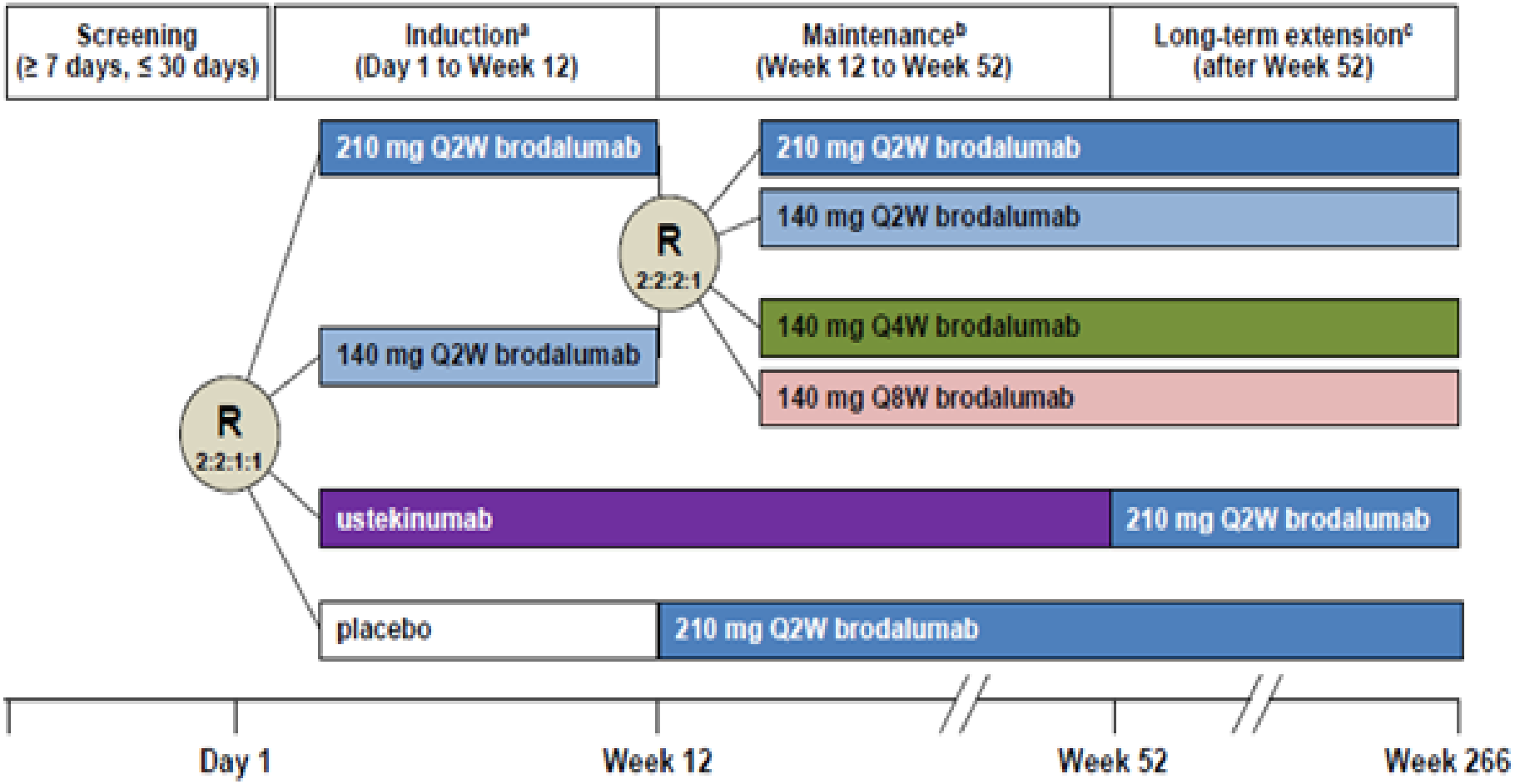


Multiple dose Study

Brodalumab dose	Median IL-17A concentration (pg/mL)	
	Baseline	Pre-dose At Steady State
140 mg Q2W	0.37	0.76-0.92
210 mg Q2W	0.48	1.44-1.62

EFFICACY OVERVIEW

Study Design for Trials 103/104

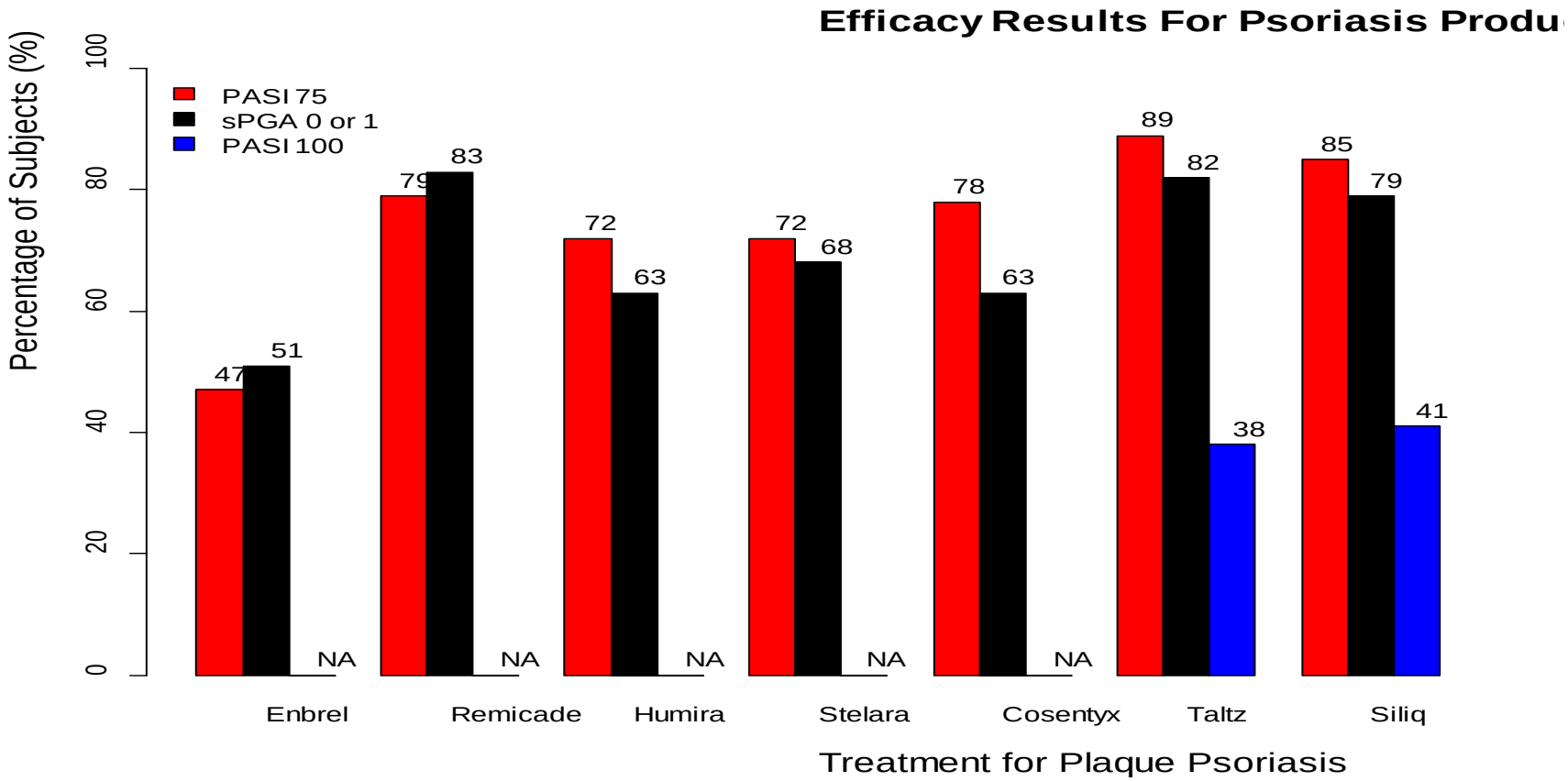


Study 102 (without active comparator) is not described here

Week 12 Efficacy

		Brodalumab 210 mg	Brodalumab 140 mg	Placebo	Ustekinumab
Trial 102		N=222(%)	N=219(%)	N=220(%)	N/A
	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)	
	sPGA of 0 or 1	168 (76)	118 (54)	3 (1)	
Trial 103		N=612(%)	N=610(%)	N=309(%)	N=300(%)
	PASI 75	528 (**86**)	406 (67)	25 (8)	210 (70)
	PASI 100	272 (44)	157 (26)	2 (0.6)	65 (22)
	sPGA of 0	274 (45)	157 (26)	2 (0.6)	65 (21)
	sPGA of 0 or 1	481 (79)	354 (58)	12 (4)	183 (61)
Trial 104		N=624(%)	N=629(%)	N=315(%)	N=313(%)
	PASI 75	531 (**85**)	435 (69)	19 (6)	217 (69)
	PASI 100	229 (**37**)	170 (27)	1 (0.3)	58 (19)
	sPGA of 0	229 (37)	170 (27)	1 (0.3)	58 (19)
	sPGA of 0 or 1	497 (80)	377 (60)	13 (4)	179 (57)

Week 12 Efficacy Across Psoriasis Programs



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.

SAFETY ASSESSMENT

Common Adverse Reactions (Induction Period)

Adverse Reactions (≥ 1.0%)	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)

Induction period = first 12 weeks (placebo-controlled)

Serious Adverse Events (1st Dose to End of Study)

	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)**
SIB (All)	**4 (0.6)**	**12 (0.3)**	**4 (0.9)**	**10 (0.4)**	**30 (0.3)**
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)	3 (0.4)	17 (0.3)	1 (0.2)	11 (0.5)	32 (0.4)

Specific Safety Issues

- **Infections**
- **Malignancies**
- **Neutropenia**
- **Worsening of Crohn's disease** (one subject discontinued due to new Crohn's onset)
- **Immunogenicity** (anti-brodalumab antibodies)
- **Suicide Ideation and Behavior** (SIB)
- **Cardiac disorders** (MACE)

Events of Special Interest (Week 52-End of Study)

Exposure-adjusted event rates (per 100 subject-years)	**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)	100 (1.8)	104 (1.2)
Ischemic cerebrovascular disease	1 (0.2)	7 (0.2)	12 (0.2)	21 (0.2)
Ischemic Heart Disease	5 (1.0)	40 (1.2)	56 (1.0)	85 (1.0)
Malignancies	13 (2.6)	30 (0.9)	44 (0.8)	43 (0.5)

Rates of Serious Infections Across Biologics

Rates of Serious Infections with Exposure to Specific Products in Psoriasis Trials							
Product	**Patient N**	**Exposure PY**	**Serious infections N**	**Active TB N**	**Fatal infections N**	**Serious infections/ 100 PY**	**Active TB/ 100 PY**
Brodalumab (with 120 Day Safety Update)	4,464	9174	109	n/a	0	1.19	n/a
Adalimumab	1,468	4,069	53	6	0	1.30	0.15
Etanercept	1,160	2,052	26	0	0	1.27	0
Infliximab	1,654	1,260	23	2	1	1.83	0.16
Ixekizumab	4,209	6,480	87	n/a	0	1.34	n/a
Secukinumab	3,430	2,725	40	0	0	1.47	0
Ustekinumab	3,117	6,791	75	0	3	1.10	0

Suicidal Ideation and Behavior (SIB) in Brodalumab Development Programs

- 34 subjects had 39 SIB events
  - **6 completed suicides***
    - 4 in psoriasis program **(39M, 56M, 56M*, 58M)**
    - 2 in other development programs:1 in RA (**42F**) and 1 in PsA (**57M**)
- All studies were terminated on May 22, 2015
  - A total of 3237 psoriasis subjects were in the study at the time
  - 2 SIB events occurred following program termination

*One suicide adjudicated as indeterminate by investigator/wife

Summary Patient Profiles Completed Suicide

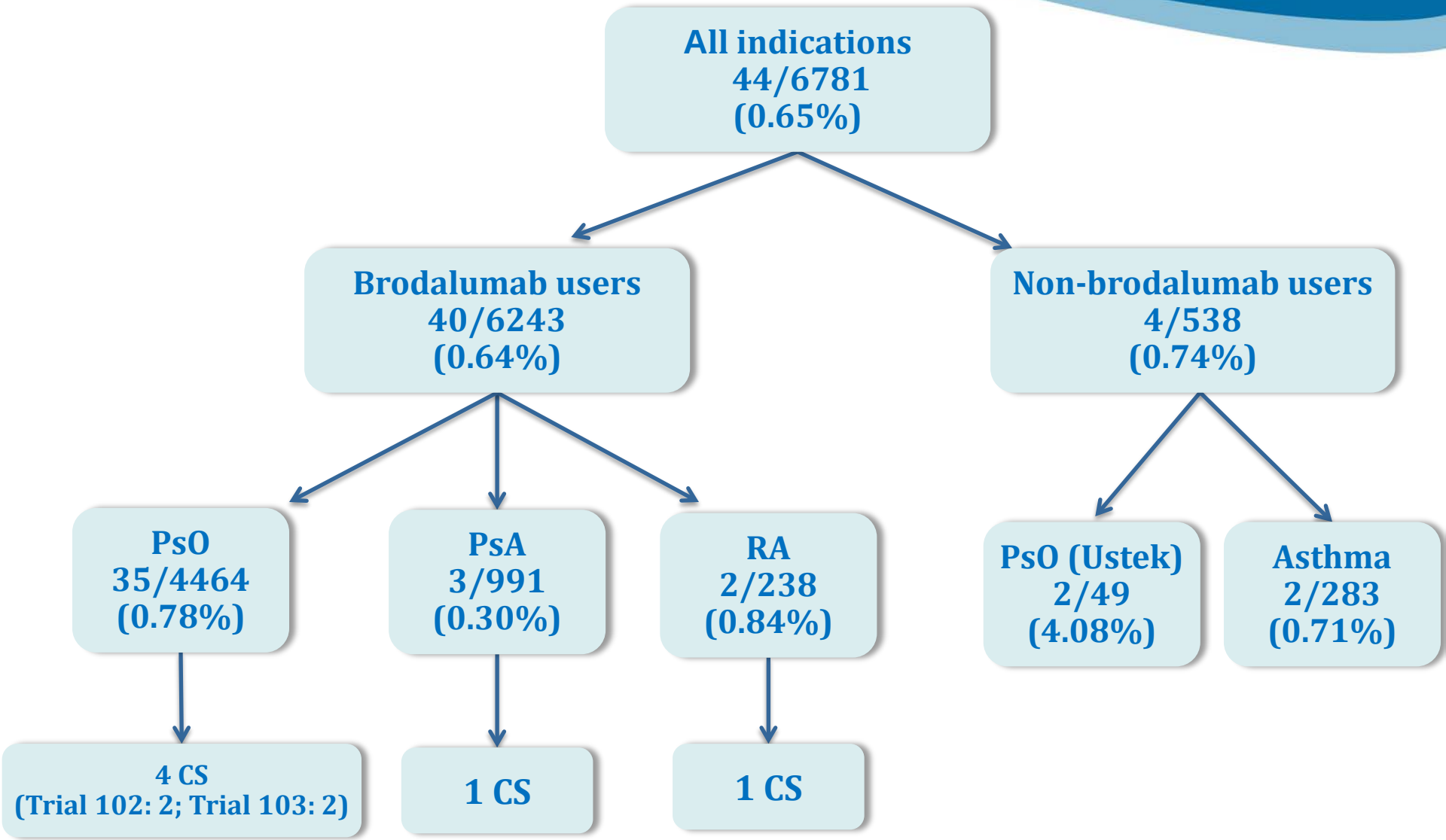
Indication	BW (kg)	Age (yr)	Sex	Race	Dose	PASI response	SIB event from the first active dose (days)	SIB event from the last dose (days)	Completed suicide
Psoriasis	**73**	56	Male	Asian	P→210 mg Q2W	100%	97 (180*)	14	Intentional overdose
Psoriasis	**55**	58	Male	White	P→210 mg Q2W	100%	329 (415*)	58	By hanging
Psoriasis	112	54	Male	White	210 mg Q2W	100%	846	19	Jumping off the roof
Psoriasis	**62**	39	Male	White	P→210 mg Q2W	73%	140 (224*)	27	Not disclosed
RA	121	42	Female	White	70 mg Q2W →210 mg Q2W	--	231	**7**	Not disclosed
PsA	90	57	Male	White	140 mg Q2W →280 mg Q2W →210 mg Q2W	--	965	41	Self-inflicted gun

*Study day in psoriasis trial (note its difference from the "days from the first active dose" due to the placebo treatment period)

Biostatistical Analysis of SIB

Ling Lan, PhD
Biostatistics Reviewer
Division of Biostatistics VII,
Office of Biostatistics,
CDER, FDA

Distribution of SIB



1 of the 35 SIBs in brodalumab users occurred while the subject received ustekinumab

CS: completed suicide; PsA: psoriatic arthritis; RA: rheumatoid arthritis

Baseline Demographics and Characteristics in Safety Population

By original treatment assignment

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

SIB Incidence During the 12-week Placebo-controlled Phase of PsO Trials

SIB Events	Brodalumab n = 3066	Placebo n = 879	Ustekinumab n = 613
Number (%)	1 (0.03%)	0	0

SIB Incidence and Time-adjusted Incidence Rates During the 52-week Active-controlled Phase 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	
Incidence rate*	0.2	0	0.6	
	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 subject-years

SIB Incidence and Time-adjusted Rates in PsO Trials (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	
Incidence rate*	0.33	0.9	8.66	
	Brodalumab + Brodalumab after Ustekinumab n = 4464			
Number (%; 95% CI)	35** (0.78; 0.63–1.25)			
Follow-up time	9173.9			
Incidence rate*(95% CI)	0.38 (0.27–0.53)			

* per 100 subject-years
** 1 of the 7 SIBs in the brodalumab after ustekinumab arm, and consequently, 1 of the 35 SIBs in brodalumab users occurred while the subject received ustekinumab

SIB in Brodalumab Users by Baseline Depression or eC-SSRS 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			
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

eC-SSRS Response through Week 52 in Safety Population of Trials 103 & 104

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

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

Maximum PHQ-8 Score through Week 52 in Safety Population of Trials 103 & 104

Maximum PHQ-8 assessment	Brodalumab n (%)	Ustekinumab n (%)	All subjects n (%)
All subjects (N)	160	78	474
0 to 4 (None to Minimal)	305 (83)	69 (88)	462 (83)
5 to 9 (Mild)	50 (14)	6 (8)	76 (14)
10 to 14 (Moderate)	9 (2)	2 (3)	14 (3)
≥ 15 (Moderately severe to severe)	4 (1)	1 (1)	6 (1)

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

Biometrics VII Conclusions on SIB

- The limited duration of placebo-controlled phase did not provide long enough exposure time to observe or compare SIB between brodalumab and placebo arms
- Brodalumab users with history of suicidality had an approximately 18-fold increase in SIB incidence rate than users without history

Division of Pharmacovigilance
Review of SIB

Robert L. Levin, MD
Director
Division of Pharmacovigilance I (DPV-I)
Office of Pharmacovigilance and Epidemiology,
Office of Surveillance and Epidemiology,
CDER, FDA

Information Reviewed to Assess Suicide Signal

- SIB complex to assess, relatively rare events; requires assessment of all available information for perspective

- Medical literature re: Psoriasis and Psychiatric Morbidity, impact on Quality of Life and patients' experiences

- Controlled phases of brodalumab studies, neuropsychiatric adverse event (NPAE) data

- Non-controlled, open-label phases, NPAE data

Psoriasis Morbidity in Psoriasis

- Psoriasis patients: (by Structured Diagnostic Assessment, MINI)*
  - Any psychiatric disorder 45%
  - Dysthymia 29% (chronic depression)
  - Major depression 15%
  - Suicidality 13%
  - Alcohol Abuse, Dependence 7%
  - Generalized Anxiety disorder 5%; Panic disorder 2%
  - >1 psychiatric disorder 8%

- *These and many other psychiatric disorders are risk factors for SIB, including completed suicide*

*Singh et al. 2016; Northern India population

Psychiatric Morbidity (continued)

- Psoriasis patients have increased rates of SIB
  - Ranges in literature: 7% to 21% have suicidality

  - UK retrospective cohort study, Hospital Episode Statistics[1]
    - Self-harm including suicide, RR = 1.6 [95% CI 1.5-1.7]
    - 4th highest RR for non-psychiatric chronic medical conditions

- Increased risk for depression, anxiety, suicidality
  - Cohort study UK General Practice Research Database (GPRD)[2]
  - Hazard Ratios: 1.39, 1.31, 1.44, respectively

[1] Singhal et al. 2014

[2] Kurd et al. 2010

Analyzing Spectrum of Neuropsychiatric Adverse Events (NPAE)

- Drugs causing CNS AEs typically cause a spectrum of neurological, cognitive, and psychiatric AE, rather than single type of adverse event.
  - Often, a cluster of several types of CNS AEs occur in a single patient
  - Examples: antidepressants, antiepileptics, antivirals

- Generally, this was not the case in brodalumab studies
  - Very few neuropsychiatric AE in all treatment groups in controlled studies
  - Few differences among treatment groups
  - However, there was no prospective, directed assessment of such AEs

- Most subjects with NPAEs had history of, or current psychiatric disorder or treatment.
- Most NPAEs were isolated, transient, did not lead to discontinuation or treatment

Controlled Phase: Exposure-adjusted Rates of Psychiatric Adverse Events

Adverse Event	Placebo 195 Sub-yrs N = 879 (r)	Ustekinumab 140 Sub-yrs N = 613 (r)	Brodalumab 688 Sub-yrs N = 3066 (r)
Depression	5 (2.6)	3 (2.2)	14 (2)
Depressed mood	1 (0.5)	2 (1.4)	3 (0.4)
Anhedonia	0	1 (0.7)	0
Anxiety	2 (1)	3 (2.2)	13 (1.9)
Panic attack	0	0	1 (0.1)
Claustrophobia	1 (0.5)	0	0
Stress	1 (0.5)	0	3 (0.4)
Mood swings	0	0	3 (0.4)
Bipolar disorder	1 (0.5)	0	1 (0.1)

Controlled Phase: Exposure-adjusted Rates of Psychiatric Adverse Events-2

Adverse Event	Placebo 195 Sub-yrs N = 879 (r)	Ustekinumab 140 Sub-yrs N = 613 (r)	Brodalumab 688 Sub-yrs N = 3066 (r)
Suicide attempt	0	0	2 (0.3)
Emotional disord.	1 (0.5)	0	0
Confusional state	0	0	1 (0.1)
Insomnia	6 (3.1)	4 (2.9)	18 (2.6)
Sleep disorder	0	0	1 (0.1)
Irritability	0	0	1 (0.1)
Libido decreased	0	0	5 (0.7)
Libido increased	0	0	1 (0.1)
Apathy	1 (0.5)	0	0
Hallucination, olfactory	0	0	1 (0.1)

Controlled Phase: Exposure-adjusted Rates of Neurologic Adverse Events

Adverse Event	Placebo 195 Sub-yrs N = 879 (r)	Ustekinumab 140 Sub-yrs N = 613 (r)	Brodalumab 688 Sub-yrs N = 3066 (r)
Headache	33 (17)	25 (18)	178 (26)
Migraine	2 (1)	3 (2.2)	10 (1.5)
Tension headache	1 (0.5)	2 (1.4)	2 (0.3)
Cluster headache	0	0	2 (0.3)
Paresthesia	1 (0.5)	4 (2.9)	20 (2.9)
Hyperesthesia	0	0	2 (0.3)
Hypoesthesia	2 (1)	1 (0.7)	4 (0.6)
Burning sensation	3 (1.5)	0	3 (0.4)
Neuralgia	0	0	2 (0.3)

Controlled Phase: Exposure-adjusted Rates of Neurologic Adverse Events-2

Adverse Event	Placebo 195 Sub-yrs N = 879 (r)	Ustekinumab 140 Sub-yrs N = 613 (r)	Brodalumab 688 Sub-yrs N = 3066 (r)
Somnolence	1 (0.5)	0	5 (0.7)
Lethargy	2 (1)	0	0
Parasomnia	0	1 (0.7)	1 (0.1)
Delayed sleep	0	1 (0.7)	0
Sleep phase d/o	1 (0.5)	0	0
Consciousness alt.	0	0	1 (0.1)
Amnesia	0	1 (0.7)	0
Balance disorder	0	0	1 (0.1)
Cognitive disorder	0	0	1 (0.1)

Controlled Phase: Exposure-adjusted Rates of Neurologic Adverse Events-3

Adverse Event	Placebo 195 Sub-yrs N = 879 (r)	Ustekinumab 140 Sub-yrs N = 613 (r)	Brodalumab 688 Sub-yrs N = 3066 (r)
Dizziness	4 (2.1)	3 (2.2)	17 (2.5)
Syncope	1 (0.5)	1 (0.7)	2 (0.3)
Hypertonia	0	1 (0.7)	2 (0.3)
Hypotonia	1 (0.5)	0	0
Attention d/o	2 (1)	0	0
Tremor	0	1 (0.7)	2 (0.3)
Encephalopathy	0	0	1 (0.1)
Formication	0	0	1 (0.1)
Dyskinesia	0	0	1 (0.1)

Hospital Anxiety-Depression Scale (HADS) Scores (Trial 102)*

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

*Trial 102 subjects w/ baseline severity moderate-severe depression or anxiety

DPV Conclusions

- There is uncertainty re: potential relationship between brodalumab and Completed Suicide, and other SIB and neuropsychiatric AEs.
- From brodalumab study data, we currently can't conclude whether or not these are drug-related risks. Possibly these are drug-related, possibly not.
- Completed suicide is obviously a severe outcome. We must consider the application and regulatory actions carefully.

DPV Recommendations

- Consider approval of brodalumab for: (1) Psoriasis (broadly), or (2) as second-line treatment of Psoriasis in patients with inadequate response to other biologic treatments for psoriasis.
- Discuss the suicide and SIB signal in labeling in detail (Warning). Clarify that there is uncertainty: possibly a drug-related risk, possibly not
- Consider risk mitigations strategies. An SIB assessment tool could possibly partially mitigate the risks, but probably could not prevent all suicides. We have difficulty predicting suicide.
- Recommend not excluding psychiatric patients from treatment with brodalumab: haven't established a drug-related risk; many psoriasis patients have psychiatric morbidity.

Division of Epidemiology-I
Review of SIB

Andrew Mosholder, MD, MPH
Medical Officer, Division of Epidemiology I (DEPI-I)
OPE, OSE, CDER, FDA

Sukhminder K. Sandhu, PhD, MPH, MS
Simone P. Pinheiro, ScD, MSc
Gabriella Anic, PhD, MPH

Division of Epidemiology-I Evaluation of Suicidal Ideation and Behavior (SIB)

- Challenges in evaluating risk of suicide with brodalumab
  - Suicides occurred in brodalumab clinical trials, but none during placebo-controlled periods
  - SIB events were rarely reported in placebo-controlled periods
    - Only 1 event, a suicide attempt by a brodalumab-treated subject
    - Monitoring for SIB not implemented until after the placebo-controlled portions of the trials were completed
  - Limited sample size and duration of exposure for placebo and active control groups prohibited meaningful comparisons within the brodalumab development program itself
- Accordingly, it was necessary to make external comparisons to trial data for other psoriasis products

DEPI-I Evaluation of Suicidal Ideation and Behavior (SIB): Methods

- Clinical trial data extracted from submissions of recent psoriasis products, and compared to brodalumab trial data
  - Data on suicides, suicide attempts, and suicidal ideation abstracted from available sources
  - Pooled summary data only, no subject-level data
- Caveats
  - External (historical) comparisons not optimal
  - Data subject to heterogeneity in patient characteristics, follow-up methods, time of trials, & ascertainment of suicidal adverse events
  - Not a subject-level meta-analysis
  - Safety data specific to psoriasis subjects not always available

Rates of Suicide with Psoriasis Products

Dataset, indication	N	Exposure Patient - years	Completed suicides, N	Suicides/ 100,000 PY
Brodalumab, all (updated from 120d SU)	6,243	10,438	6**#	57.5
Brodalumab, Ps trials (from 120d SU)	4,464	9162	4**	43.7
Ixekizumab, Ps‡	4,209	6,480	0	0
Secukinumab Ps, PsA‡	3,928	3,225	0*	0
Adalimumab, Ps	1,468	4,069	1**	24.6
Etanercept, Ps	1,807	2,773	0	0
Infliximab, Ps	1,564	1,263	0	0
Apremilast, Ps, PsA, RA‡	2,401	1,483	0†	0
Unapproved biologic, Ps	2,520	3,011	2**	66.4
Ustekinumab, Ps	3,117	6,791	1	14.7
Pooled w/o brodalumab, apremilast	18,613	27,612	4	14.5

*There was 1 suicide during screening for a Ps trial , and 1 suicide in an ankylosing spondylitis trial (placebo)
**Includes suicides during post-treatment follow-up †2 suicides occurred on placebo ‡Adjudicated with C-CASA
#4 cases were adjudicated with C-CASA, and 1 was adjudicated as indeterminate
PY patient-years, Ps psoriasis, PsA psoriatic arthritis, RA rheumatoid arthritis , 120d SU 120-day Safety Update

Comparison of Brodalumab Trial Data to Sponsor's Systematic Review of Psoriasis Trials

Dataset	Subjects N	Exposure PY	Completed suicides N	Suicides/100,000 PY (95% CI)
Brodalumab, all trials	6,243	10,438	6	57 (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).

PY person-years

Comment: Several-fold higher suicide rate in brodalumab clinical trials compared to other psoriasis biologics combined

Comparison of Brodalumab Trial Data to Sponsor's Systematic Review of Psoriasis Trials (2)

As a thought experiment, consider the suicide rate from sponsor's systematic review of Phase III-IV psoriasis biologics trials as the expected rate

- Brodalumab psoriasis trials showed a 2.3-fold higher than expected suicide rate
  - 44 versus 19 per 100,000 patient years
  - Equivalent to roughly 1 excess suicide per 4054 person-years of use
- All brodalumab trials combined showed a 3-fold higher than expected suicide rate
  - 58 versus 19 suicides per 100,000 patient years
- Equivalent to roughly one excess suicide per every 2598 person-years of use

Psychiatric Adverse Events During 12-week Double Blind Period (Source: BLA SIB supplement)

Table 24 **Subject incidence of psychiatric AEs occurring at ≥0.1% in the all-brodalumab group during initial double-blind period - Pool A; MA Data Cutoff - Integrated Safety Analysis Set - Psoriasis Subset**

			Brodalumab		
Preferred Term	**Placebo (N=879) n (%)**	**Ustekinumab (N=613) n (%)**	**140 mg Q2W (N=1491) n (%)**	**210 mg Q2W (N=1496) n (%)**	**All (N=3066) n (%)**
Psychiatric disorders	**16 (1.8)**	**12 (2.0)**	**30 (2.0)**	**31 (2.1)**	**61 (2.0)**
Insomnia	6 (0.7)	4 (0.7)	7 (0.5)	10 (0.7)	17 (0.6)
Depression	5 (0.6)	3 (0.5)	9 (0.6)	5 (0.3)	14 (0.5)
Anxiety	2 (0.2)	2 (0.3)	10 (0.7)	3 (0.2)	13 (0.4)
Libido decreased	0 (0.0)	0 (0.0)	2 (0.1)	3 (0.2)	5 (0.2)
Depressed mood	1 (0.1)	2 (0.3)	2 (0.1)	1 (0.1)	3 (0.1)
Mood swings	0 (0.0)	0 (0.0)	1 (0.1)	2 (0.1)	3 (0.1)
Stress	1 (0.1)	0 (0.0)	0 (0.0)	3 (0.2)	3 (0.1)

MedDRA v. 17.1; N=subjects in Studies 20090062, 20120102, 20120103, 20120104 with ≥ 1 dose of investigational product
n=number of subjects reporting ≥1 occurrence of an AE through week 12; %=n/N * 100
Treatment groups are defined as planned (randomized) treatment.
Source: Module 5.3.5.3, ISS Table 14 6.48.1.

Comment: Extremely low occurrence of psychiatric events. Possible reasons: Incomplete ascertainment of trials adverse events, absence of new events

Suicidal Adverse Events in Brodalumab Psoriasis Trials Before and After Implementation of Electronic Columbia Suicide Severity Rating Scale (eC-SSRS) Monitoring

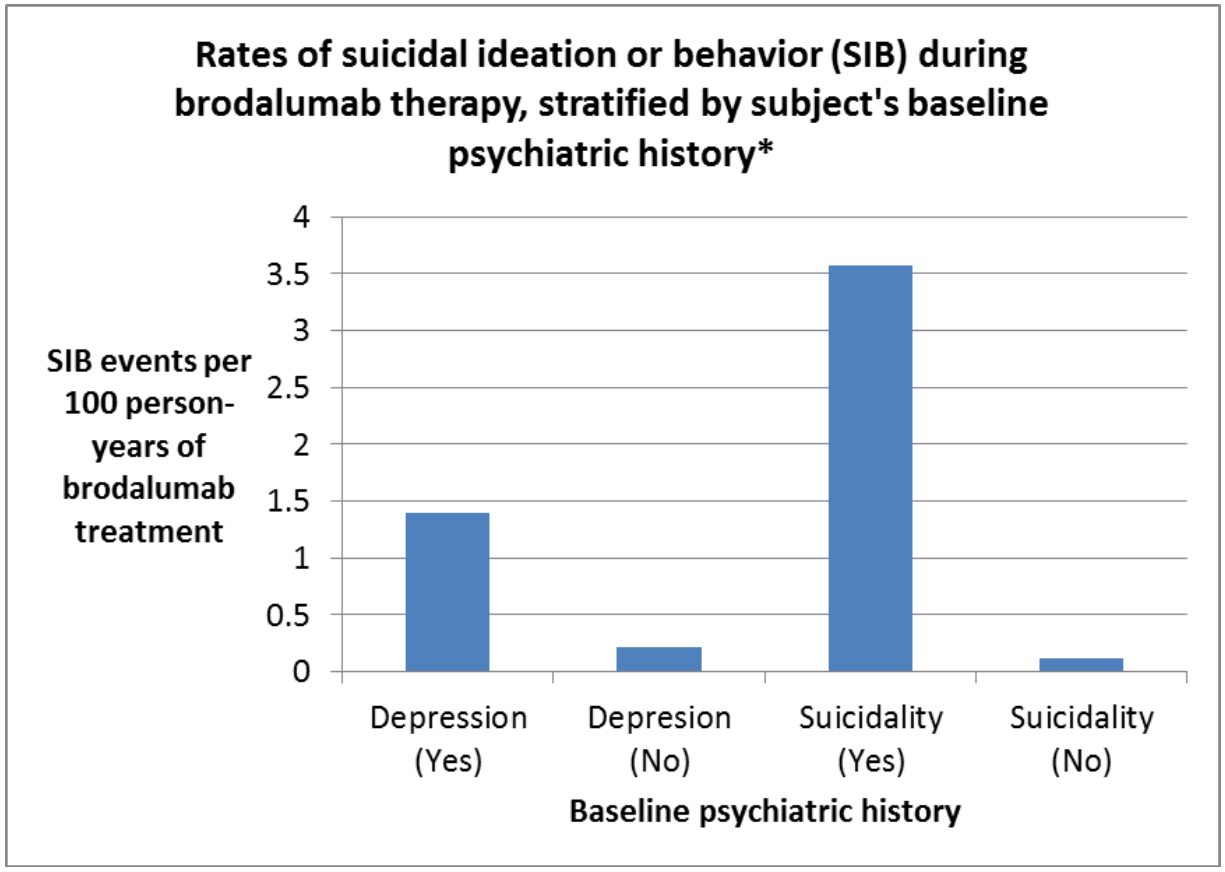
Event	Pre eC-SSRS N=4464 PY 5383.3		Post eC-SSRS N=3823 PY 2530.2	
	n	Rate/100 PY	n	Rate/100 PY
Completed suicide	3	0.06	1	0.04
Any suicidal behavior	6	0.11	5	0.20
Suicidal ideation	3	0.06	15	0.59

Source: SIB supplement Table 32.

PY person-years. Includes all follow-up observation time.

Comment: eC-SSRS monitoring greatly improved SIB detection; unclear whether monitoring prevented suicide attempts/suicides.

Two subjects had negative eC-SSRS shortly before their suicides.



*Past history determined from baseline evaluation and "lifetime" response category for suicidality on eC-SSRS (sponsor's analysis). Includes all follow-up observation time. Source: BLA SIB supplement, Table 22

Comment: Among brodalumab-exposed, past psychiatric history profoundly influenced rate of SIB

DEPI-I Conclusions for SIB Analysis

- Several-fold higher suicide rate in brodalumab clinical trials compared to other psoriasis biologics combined
- Insufficient number of suicidal events in double blind trials for meaningful comparison to placebo
- Detection of nonsuicidal psychiatric adverse events appears to have been incomplete
- eC-SSRS monitoring greatly improved detection of suicidal ideation, and perhaps suicidal behavior; unclear whether monitoring prevented suicide attempts/suicides
- Past psychiatric history profoundly influenced rate of suicidal events

DEPI-1 SIB Recommendations

1. To the extent there is "insufficient information about the drug to determine whether the product is safe for use," [21 CFR 314.125 (b) (4)], consider CR
2. If approved
    a) Restricting use to patients without psychiatric risk factors would reduce SIB events among brodalumab users (regardless of causality)
    b) eC-SSRS or similar monitoring would improve detection of SIB, facilitate referral
    c) Appropriate labeling & Medication Guide
    d) No postmarketing observational study for SIB events at this time, given the limitations of electronic databases for measuring suicidal outcomes

Division of Psychiatric Products Review of SIB

Jean Kim, MD, MA
Medical Officer
Division of Psychiatry Products (DPP)
ODE I, OND, CDER, FDA

DPP Consult

- Consulted to provide advice regarding psychiatric adverse events, including SIB, seen in brodalumab clinical trials and to clarify whether these events:
  - Were a primary drug effect
  - Reflect background occurrence of these events in a patient population with higher rates of depression and SIB

- In addition to implementation of the eC-SSRS and PHQ-8 midway during the psoriasis trials (maintenance phase), adverse events were retrospectively identified via the Columbia Classification Algorithm of Suicide Assessment (C-CASA)

SIB Events During 12-Week Induction

Table 1: 12-Week Induction Phase SIB Events/Subjects

	Subjects	Events
Brodalumab	1	2
Ustekinumab	0	0
Placebo	0	0

Table 2: SIB Incidence based on the 12-week Induction Phase

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

Using a 2-tailed Fisher's exact test, the differences between the **SIB rates** for brodalumab vs. placebo **were not statistically significant** at an alpha level of 0.05 (p-values of 0.22), although power is too low to say definitively.

But We Need More Data

- **The generalizability of the 12-week finding is <u>limited</u> by**:
  - the relatively short duration of the study period
  - the overall rare incidence of SIB events
  - 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.)
  - C-CASA method used during the induction phase is less sensitive at detecting SIB events than the eC-SSRS

Observational Results in Psoriasis Studies

Table 3: Week 13 to Week 52 SIB Events/Subjects (Maintenance Phase)

	Subjects	Events
Brodalumab	6*	6*
Ustekinumab	4	5
Placebo	0	0

Table 4: Follow-Up Extension Phase (2013-2014 through March 2015)

	Subjects	Events
Brodalumab	17	20

- 4-Month Safety Report Phase (March 2015 to Nov 2015): 8 additional SIB events/subjects during this period.
- Total of 31 additional SIB subjects after the initial 12-week induction phase on brodalumab.

*1 case also was in Week 1 to 12 period

DPP Conclusions

- Review of 12-week placebo-controlled pooled data from three Phase 3 psoriasis trials for brodalumab: no significant association of SIB elevation for brodalumab versus placebo. However, generalizability of findings is limited.
- No definitive conclusions available about the relationship between brodalumab and suicidality based on current inadequate data
- Insufficiency of currently available pharmacovigilance methods to detect postmarketing events
- Unclear if REMS recommendations would be helpful in preventing suicides with uncharacterized SIB risk factors

DPP Conclusions

- 6 suicides in brodalumab trials is **higher than typically seen in DPP's large psychiatric drug trials** (which involve populations with higher psychiatric morbidity than patients with psoriasis)

- As per literature, no effective screening scale exists for prevention of suicide; REMS recommendations for increased screening may not be helpful in reducing SIB events, if true drug association exists.

- At least four of the brodalumab trial subjects who committed suicide had no disclosed prior psychiatric history and 2/2 screened, showed no findings on eC-SSRS

DPP Recommendations

- Sponsor conduct an additional **active-controlled, parallel group study with brodalumab prior to approval**
  - Active control agent should be a psoriasis agent with low SIB event risk
  - Focus on frequent psychiatric symptom monitoring, especially SIB but also depressive symptoms during the proposed study
  - Can help clarify relationship between brodalumab treatment and SIB, and risk factors to inform a future REMS

DPP Recommendations

- If negative, REMS might even be unnecessary
- Pre-marketing study, given that other safe and effective psoriasis drugs already on market without known SIB risk
- Will likely have to be a large study of considerable length due to low SIB incidence/powering
- DPP is willing to work with FDA dermatology experts, epidemiologists, and statisticians in designing such a trial

Biostatistical Analysis of Major Adverse Cardiovascular Events

Gary Chiang, MD, MPH
Medical Officer
DDDP, ODE III, OND, CDER, FDA

Exposure and Fatal Outcomes PsO Trials
Major Adverse Cardiovascular Outcomes (MACE)

- MACE is defined as CV death, non-fatal MI, or non-fatal stroke that occurred after the first treatment dose and < 42 days after the last treatment dose

- In All Phase 3, 4363 subjects were exposed to ≥1 dose of brodalumab

- 9 adjudicated (CEC) as MACE Deaths
  - 6 sudden deaths (5 brodalumab, 1 ustekinumab)
  - 2 Stroke
  - 1 undetermined

Baseline Demographics and Characteristics of Phase 3 Safety Population

By original treatment assignment

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)

MACE Incidence During the 12-week Placebo-controlled Period of PsO Trials

MACE	Brodalumab n = 2908	Placebo n = 842	Ustekinumab n = 613
Number (%)			
Total	3 (0.10)	1 (0.12)	0
CV death	0	0	
MI	2 (0.07)	1 (0.12)	
Stroke	1 (0.03)	0	

MACE During the 52-week Active-controlled Period of PsO Trials

MACE	Brodalumab n = 3711	Brod after Ustek n = 124	Ustekinumab n = 489	Placebo n =39
Number (%)				
MACE	25† (0.7)	0	2 (0.4)	0
CV death	1 (0.1)	0	0	0
MI	16 (0.4)	0	2 (0.4)	0
Stroke	5 (0.1)	0	0	0
Follow-up time	3297.2	75.5	494.8	
Incidence rate*	0.8	0	0.4	

MACE	Brodalumab + Brodalumab after Ustekinumab n = 3835
Number (%; 95% CI)	25 (0.7, 0.46–1.02)
Follow-up time	3372.7
Incidence rate* (95% CI)	0.7 (0.48–1.10)

†One subject 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

MACE Incidence and Time-adjusted Rates in PsO Trials (Day 1 to end of 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	

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 occurred before the first dose of brodalumab and the subject was originally assigned in the placebo arm; and 3) one CV death 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

MACE in Brodalumab Users by Age and Cardiovascular Disease History

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**

Statistical Conclusions

- The limited duration of placebo-controlled phase did not provide long enough exposure time to observe or compare MACE between brodalumab and placebo arms
- 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
- Brodalumab users with a history of cardiac or vascular disorder had a 4.7-fold increase in incidence rate of MACE compared to users without history

Division of Cardiovascular and Renal Products
Review of MACE

- Data from preclinical and clinical studies for other indications did not show a MACE safety signal.
- Hemodynamic parameters in the pivotal Phase 3 psoriasis trials were stable within normal limits.
- Exposure-adjusted MACE incidence rate (0.6 per 100 subject-years) was consistent with that of the general psoriasis population.
- MACE (CV death, MI, stroke) occurred in subjects predisposed to these events from medical history.
- Conclude: Evidence from the brodalumab development program does not establish an elevated risk of MACE.

Division of Epidemiology-I
Review of MACE

Andrew Mosholder, MD, MPH
Medical Officer
Division of Epidemiology I (DEPI-I)
OPE, OSE, CDER, FDA

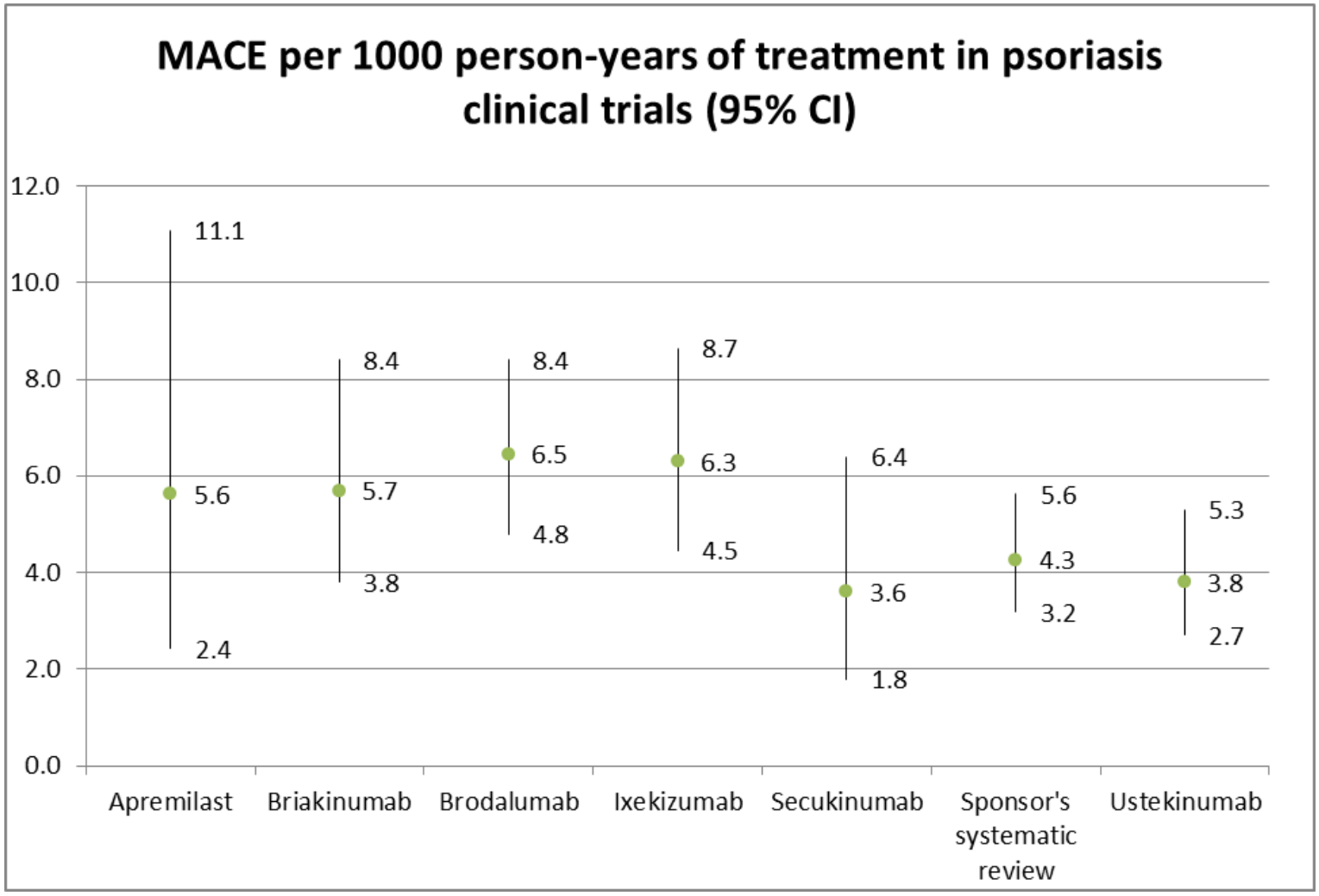
Rates of major adverse cardiovascular events (MACE) with treatment by specific products in psoriasis clinical trials

Psoriasis Product	Subjects N	Exposure PY	MACE N	CV Death N	MI N	Stroke N	MACE/ 1000 PY	CV Death/ 1000 PY	MI/ 1000 PY	Stroke/ 1000 PY	MACE outcomes adjudicated (y/n)?
***Brodalumab, Psoriasis Phase 3 trials only (*(120 Day Safety Update)**	**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) 120 day safety update; (2) Langley et al. JEADV 2013, 27, 1252–1261; (3) 120 day safety update; (4) MACE Information Request response; (5) MACE Information Request response *Categories not mutually exclusive PY person-years

Although all three products have labeling for heart failure, an analysis of MACE for adalimumab, etanercept, or infliximab could not be located. However, a recent clinical trial meta-analysis indicated a reduced rate of MACE with tumor necrosis factor inhibitors relative to active controls (Yang et al., Clinic Rev Allerg Immunol, published online 6-14-2016).

Comment: Numerically, brodalumab had highest MACE rate and CV death rate across products, though very similar to others



Comment: While the brodalumab MACE rate was highest, MACE rates were fairly similar across psoriasis products

DEPI-I Conclusions and Recommendations for MACE Analysis

- Insufficient number of MACE events in double blind trials for meaningful comparison to placebo
- While the brodalumab MACE rate was highest, MACE rates were fairly similar across psoriasis products
- Recommendations
  - Cardiovascular outcome RCT desirable but challenging
  - Postmarketing observational study may be feasible if sufficient Brodalumab uptake
  - Analysis of existing IL-17 clinical trial data among brodalumab-treated subjects, to explore possible association of IL-17 levels with MACE

Risk Management Options for Brodalumab

Jasminder Kumar, Pharm.D.
Risk Management Analyst
Division of Risk Management
Office of Surveillance and Epidemiology
CDER, FDA

Risk Evaluation and Mitigation Strategy (REMS)

- A REMS is a required risk management plan that uses risk mitigation strategies **beyond FDA-approved professional labeling**
- FDA can require applicants to develop and comply with REMS programs *if* determined necessary to ensure the benefits outweigh the risks
  - Applies to New Drug Applications (NDAs), Biologic License Applications (BLAs), and Abbreviated New Drug Applications (ANDAs)
  - REMS can be required pre- or post-approval
  - REMS are enforceable

Components of a REMS

- A REMS can include:
  - Medication Guide (MG) or Patient Package Insert for patients
  - Communication plan (CP) for healthcare providers (HCPs)
  - Elements to assure safe use (ETASU)

- Must include a timetable for submission of assessments of the REMS

Elements to Assure Safe Use (ETASU)

- Interventions or other actions HCPs may need to execute prior to prescribing or dispensing the drug to a patient

- Provides safe access for patient to drugs with known serious risks that would otherwise not be approved or would be withdrawn

ETASU Can Include…

- Certification and specialized training of **healthcare providers (HCPs)** who prescribe the drugs
- Certification of **pharmacies or other dispensers** of the drug
- Dispensing/administration of drug in **limited settings** e.g., hospitals
- Drug is dispensed/administered only with **evidence of safe-use conditions**
- Each patient using the drug is subject to certain **monitoring**
- Enrollment of treated patients in **registries**

Risk Under Consideration for a REMS

- Suicidal Ideation and Behavior (SIB)
  - Suicide complete, suicide attempt, suicide behavior and suicide ideation

Risk Management Options for SIB

- **Option 1**: Product labeling alone
  - Could include Medication Guide

- **Option 2**: REMS with communication plan (Sponsor proposed)

- **Option 3**: REMS with one or more elements to assure safe use to meet the goals and objectives of the program

Option 1: Labeling Alone for the Risk of SIB

- Labeling negotiations are ongoing

- Product sponsor's proposal:
  - Medication Guide
  - Warning and Precaution
    - Includes evaluating patients for SIB
  - No Boxed Warning

- Additional labeling options to consider:
  - Second line therapy
  - Boxed Warning

Considerations for the Use of Labeling Alone to Manage the Risk of SIB

- Second line therapy
  - May decrease the risk of SIB by limiting overall drug exposure
  - Does not eliminate the risk in an individual patient receiving medication

- Boxed Warning
  - May increase prescriber awareness of the risk of SIB
  - May provide information about patients at risk for SIB but does not provide specific tools to help HCPs identify or monitor for patients at high risk

Option 2: REMS with Communication Plan (CP) – Sponsor's Proposal

- Goals related to SIB
  - To inform healthcare providers about the potential risk of suicidal ideation and behavior in patients with psoriasis, the need to counsel patients about the risks, and consideration of referral of patients to a mental health professional
  - To educate patients to recognize the signs and symptoms of suicidal ideation and behavior, new onset or worsening depression, or other emerging mood changes, and to seek intervention should such signs emerge

- Goal related to use in patients with Crohn's Disease
  - 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

Option 2: REMS with CP– Sponsor's Proposal

- Includes:
  - Dear Healthcare Provider and Dear Professional Society letters
  - Healthcare Provider Fact Sheet and Education Brochure
  - Patient Wallet Card and Medication Guide
  - REMS Coordinating Center and REMS Website

Considerations for the Use of a CP REMS to Manage the Risk of SIB

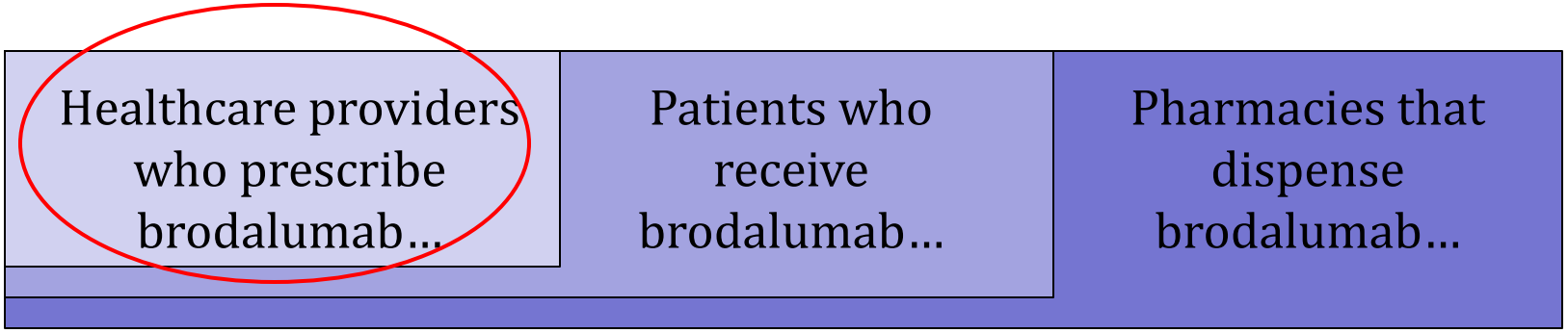
- Reinforces the risk of SIB as described in the PI
  - Communication materials use targeted risk messaging focusing on the risk of SIB
- Relatively easy to target potential prescriber specialty
  - Dermatologists and other prescriber specialties that treat psoriasis patients with similar products
- May provide additional information on how to screen patients at risk for SIB or monitor patients for SIB

Considerations for the Use of a CP REMS to Manage the Risk of SIB

- Will not ensure each prescriber has reviewed the REMS materials prior to prescribing
  - Success may be determined/limited by Sponsor's engagement
  - Provider surveys indicate 13-83% recall receiving the "Dear Healthcare Provider Letter"[1]
- Communication plans are not directed at patients, therefore will not ensure that patients will receive the risk messages before prescribed

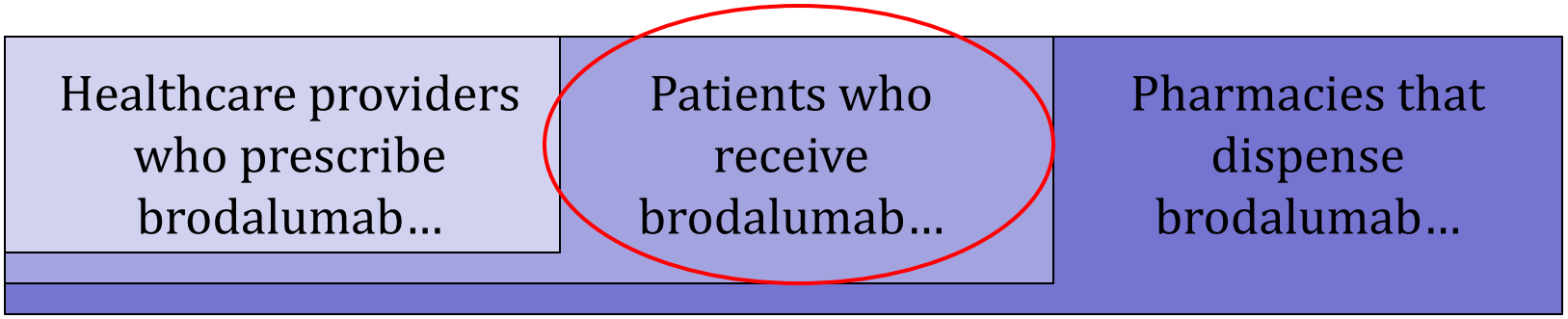
[1] FDA Risk Communication Advisory Committee, December 17, 2013; FDA Health Professional Organization Meeting, October 2012; Aggregate REMS Assessment information submitted by sponsor

Option 3: REMS with Elements to Assure Safe Use (ETASU)



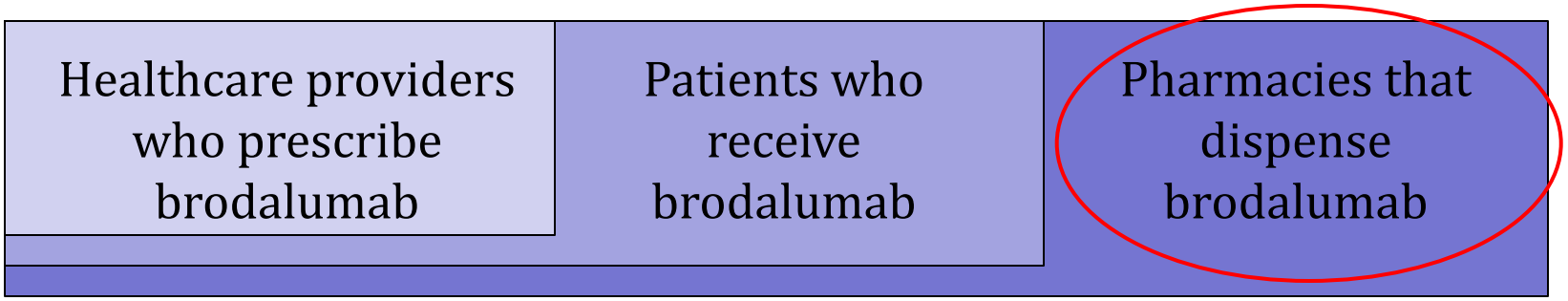
- Become certified by completing training on the risk of SIB, screening for appropriate patients, and use of self-rated scales (requires enrollment into the REMS program)
- Counsel patient on risk of SIB, assess patient's baseline status through screening, ensure proper patient selection, and enroll patient in REMS program
- Periodically monitor, assess, and/or document patient's score on self-rated scales for SIB

Option 3: REMS with ETASU



- Enroll in REMS and complete acknowledgement of the risk
- Receive counseling from the prescriber on the risks of SIB
- Agree to complete initial screening and periodic monitoring using self-rated scales at prescriber visits
- Report any signs and symptoms of SIB to prescriber

Option 3: REMS with ETASU



- Designate authorized representative to carry out certification process, enroll in the REMS, and train relevant staff
- Establish processes and procedures to verify dispensing only from certified prescribers
- Distribute REMS-related educational information to patients that inform them of the risk
- Provide counseling at the point of dispensation

Considerations for the Use of an ETASU REMS to Manage the Risk of SIB

- Ensure that prescribers are trained, informed of proper patient selection, understand the need to counsel, and screen and monitor patients for SIB
  - Identifying appropriate candidates for therapy may minimize drug exposure for an individual patient and at a population level
- Provides assurance that pharmacists are informed of the risks and opportunity for further patient counseling at the time of drug dispensation
- Ensures that patients are fully informed of risk prior to initiating therapy and may detect SIB events and potentially prevent suicide

Considerations for the Use of an ETASU REMS to Manage the Risk of SIB

- Screening of patients for SIB may decrease but will not eliminate the risk of suicide
- Screening tools may need to be assessed for appropriateness in dermatology practices
- May impact patient access or delay therapy:
  - if patients can only receive drug from a participating certified pharmacy
  - if documentation of monitoring is not received in a timely manner
- May require more frequent visits to the prescriber

Summary

- The serious risk which requires consideration for a REMS for brodalumab is SIB
- Each risk management option, beyond labeling, provides different levels of assurance that prescribers, pharmacists, and patients have been educated and understand the safe use conditions when taking brodalumab
- Risk management options would include strategies that increase awareness of the risk, but may not prevent the occurrence of suicide
  - Suicides occurred in clinical trials after implementation of similar risk mitigation strategies
- The Committee will be asked to consider whether risk management strategies beyond labeling are necessary, and if so what interventions would be able to ensure that the benefits outweigh the risks of SIB

Questions for Clarification

Dermatologic and Ophthalmic Drugs Advisory Committee Meeting

BLA 761032 SILIQ (brodalumab) for injection, for subcutaneous use for the treatment of moderate to severe plaque psoriasis

Charge to the Committee

Kendall A. Marcus, MD
Director
Division of Dermatology and Dental Products,
ODE III, OND, CDER, FDA

Benefit-Risk Assessment Regulatory Decision Making*

- Informed by science, medicine, policy, and judgment, in accordance with applicable legal and regulatory standards
- Variations in clinical and scientific judgments among FDA experts can lead to differing individual opinions and conclusions

*FDAs draft implementation plan for a Structured Approach to Benefit-Risk Assessment in Drug Regulatory Decision-Making

Issues for Consideration

- Adequacy of the safety evaluation
  - Suicidal Ideation and Behavior (SIB)
  - Major Adverse Cardiovascular Events (MACE)
- Overall benefit/risk profile of brodalumab
  - Risk management
- Post-marketing studies/trials

Approval of an Application
21 CFR 314.105 (c)

"FDA will approve an application after it determines that the drug meets the statutory standards for safety and effectiveness, manufacturing and controls, and labeling"

Safety Standard
21 CFR 314.125 Refusal to Approve an Application

(b) (2) "… do not include adequate tests by all methods reasonably applicable to show whether or not the drug is safe for use under the conditions prescribed, recommended, or suggested in its proposed labeling."

(b) (3) "The results of the test show that the drug is unsafe for use under the conditions prescribed, recommended, or suggested in its proposed labeling or the results do not show that the drug product is safe for use under those conditions."

(b) (4) "There is insufficient information about the drug to determine whether the product is safe for use under the conditions prescribed, recommended, or suggested in its proposed labeling."

Considerations for Approval with a REMS

- Seriousness of the disease or condition to be treated
- Size of the patient population
- Expected benefit of the drug
- Expected duration of treatment
- Seriousness of the known or potential adverse events

Questions and Discussion

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

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

        i. Suicide Ideation and Behavior (SIB)?

        ii. Major Adverse Cardiovascular Events (MACE)?

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

Questions and Discussion

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

    a. Yes, with labeling alone to manage the risks

    b. Yes, but only if certain risk management options for SIB beyond labeling are implemented

    c. No

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

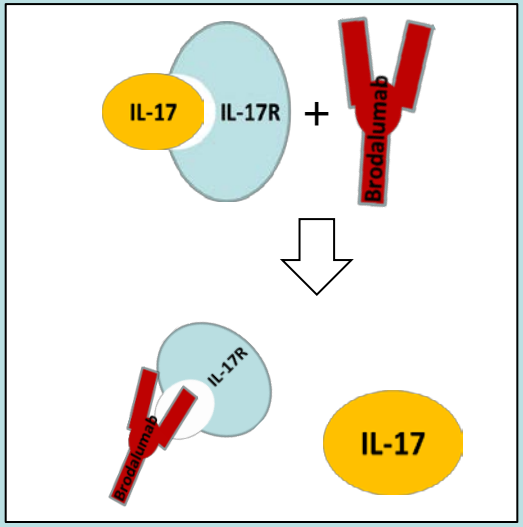
Questions and Discussion

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

BACK UP SLIDES SHOWN

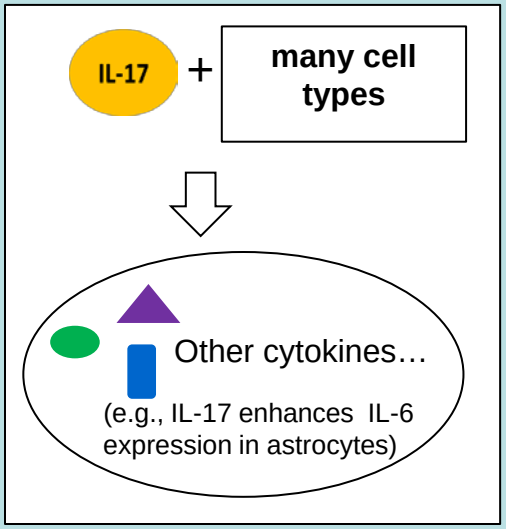
Biological Plausibility Assessment for Brodalumab and SIB

Brodalumab treatment increases serum IL-17A level in psoriasis patients



Evidence:
- Study 20120102 (Phase 3)
- Study 20110184 (DDI study)

IL-17A theoretically may induce production of other cytokines (e.g., IL-6)



Supporting data:
- Literatures

Potential associations between biological functions of cytokines with SIB:

- IL-17 and IL-6 are important in many CNS disorders characterized by neuro-inflammation
- Th17 lymphocytes and IL-17 could induce blood-brain barrier disruption
- IL-17 played a role in anxiety and depression in patients with RA.
- In a meta-analysis of 22 studies, elevated IL-6 levels were found to be associated with suicidal ideation, suicide attempts and completed suicides.

Supporting data:
- Literatures (*There are limitations in the literature data.)*