

Brodalumab

Dermatologic and Ophthalmic Drugs Advisory Committee



Introduction

Tage Ramakrishna, MD

Chief Medical Officer

President of Research and Development, Quality

Valeant

Brodalumab

Proposed Indication and Dosing

Agent

Brodalumab is a human IgG2 monoclonal antibody that selectively binds and blocks signaling through the interleukin 17 Receptor A (IL-17RA).

Proposed Indication

Treatment of moderate to severe plaque psoriasis in adult patients who are candidates for systemic therapy or phototherapy.

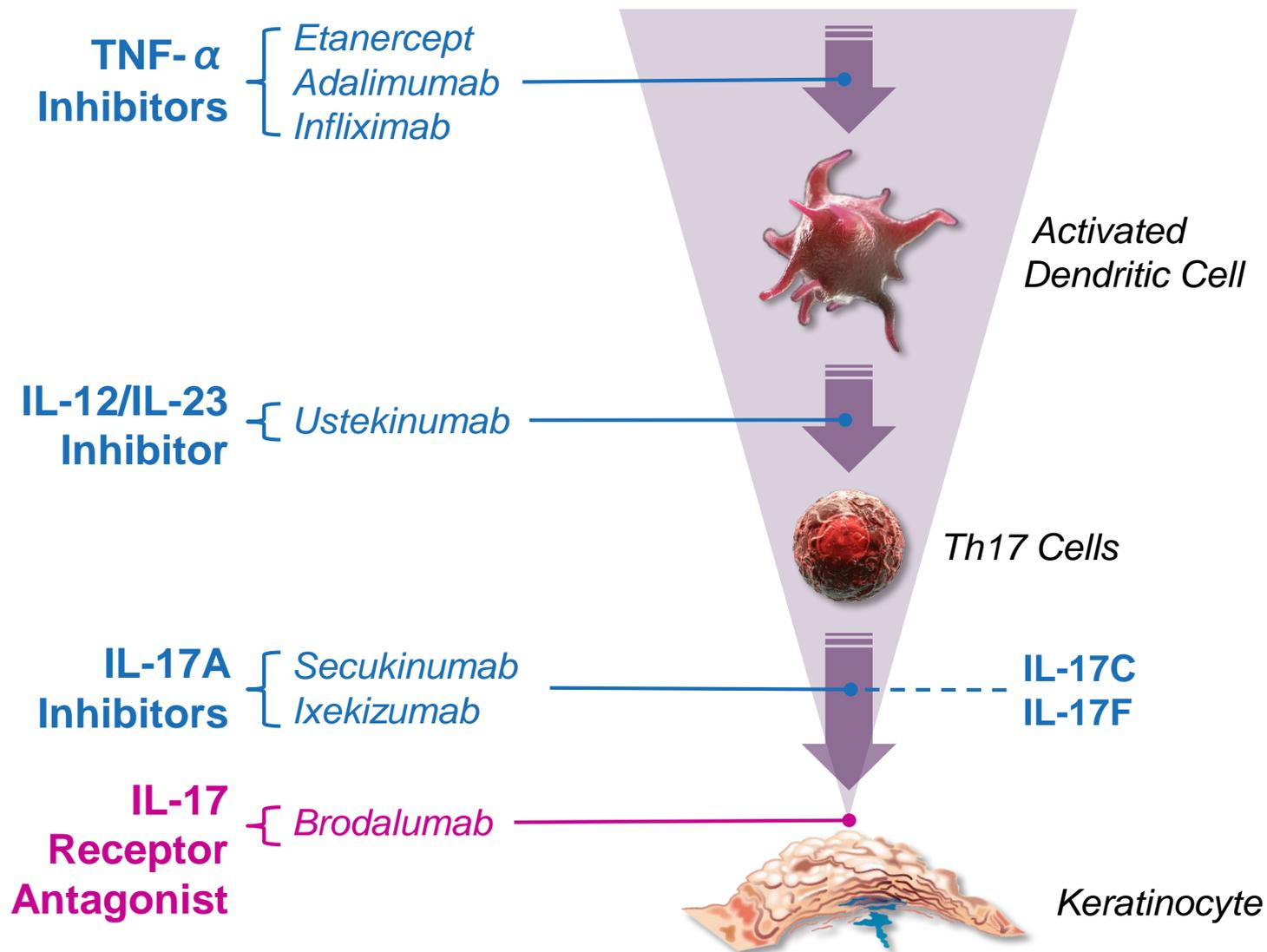
Proposed Dosing

210 mg of brodalumab administered by subcutaneous injection at Weeks 0, 1 and 2 followed by 210 mg every 2 weeks (Q2W) thereafter.

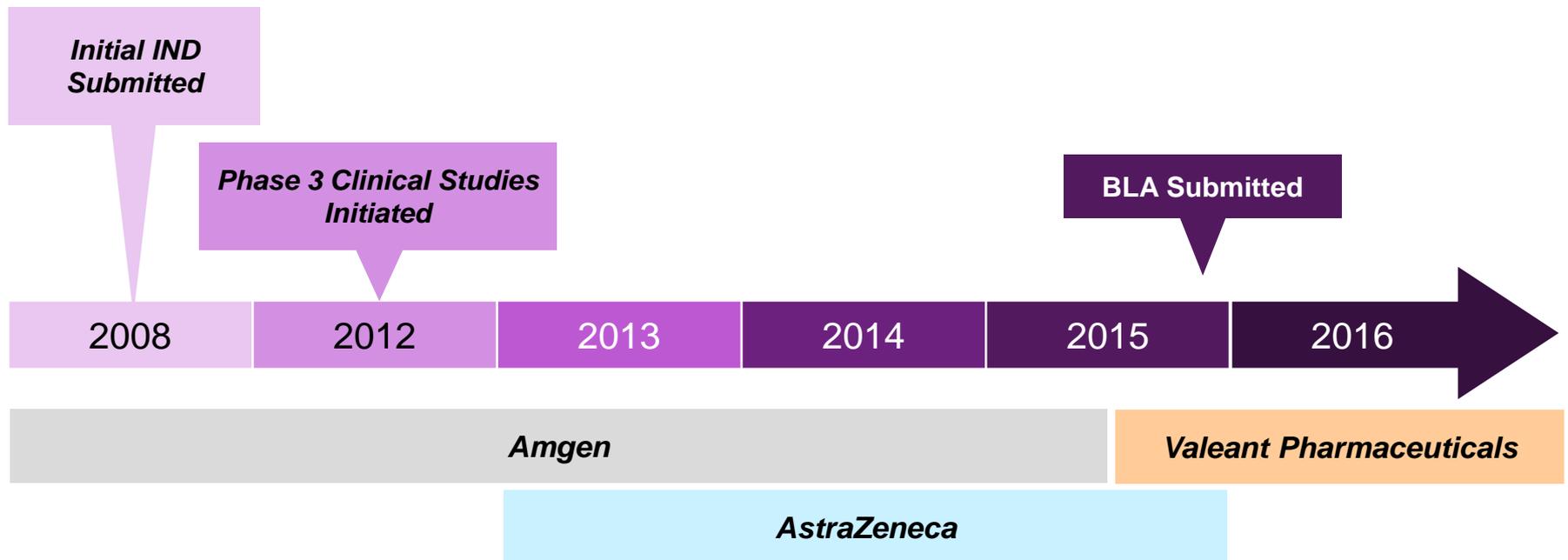
Brodalumab

- **Brodalumab has well-demonstrated, durable efficacy**
 - ▶ More than 50% of patients had complete clearance within a year
- **Safety and efficacy of brodalumab has been established through 3 large Phase 3 studies**
 - ▶ Safety database being presented is among the largest ever for a biologic
- **Brodalumab is the first biologic in psoriasis that acts directly as an IL-17 receptor antagonist**

Brodalumab's Place in the Current Therapeutic Landscape for Psoriasis



Regulatory Development Timeline



Brodalumab in Plaque Psoriasis

Clinical Development Program Overview

Phase 1

10 Studies

Healthy and Psoriasis Patients

N Enrolled/Completed

601/560

Phase 2

3 Studies

N Enrolled/Completed

530/464

Phase 3

4 Studies

N Enrolled/Completed

Psoriasis (Japan), N = 175/159

AMAGINE-1, N = 661/649

AMAGINE-2, N = 1831/1601

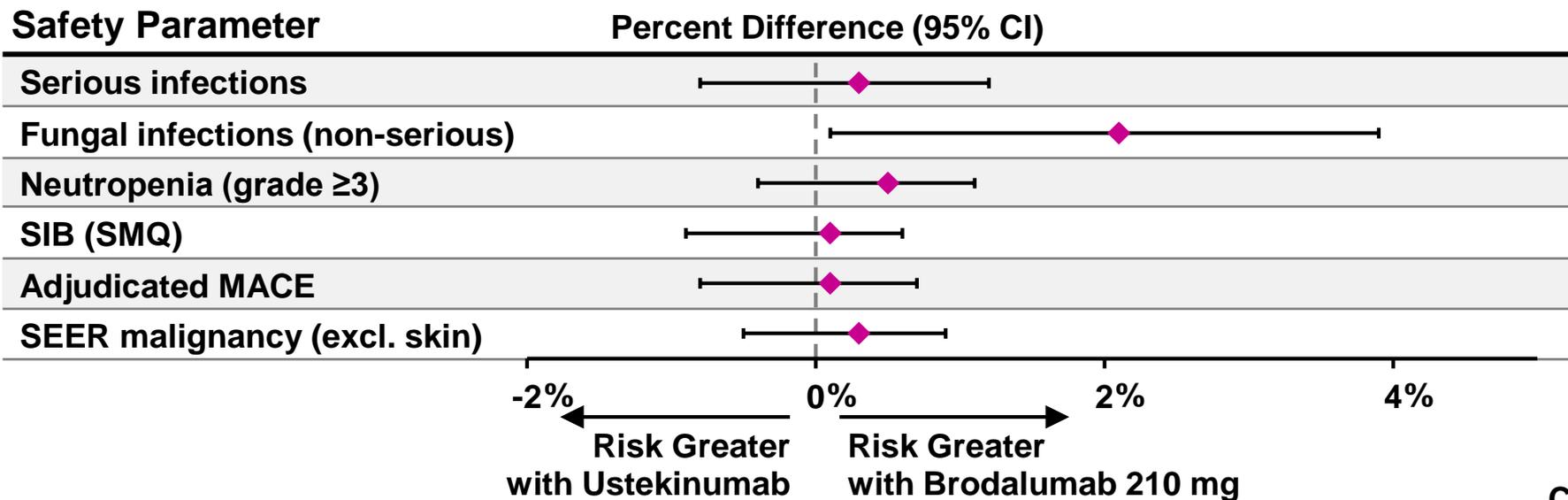
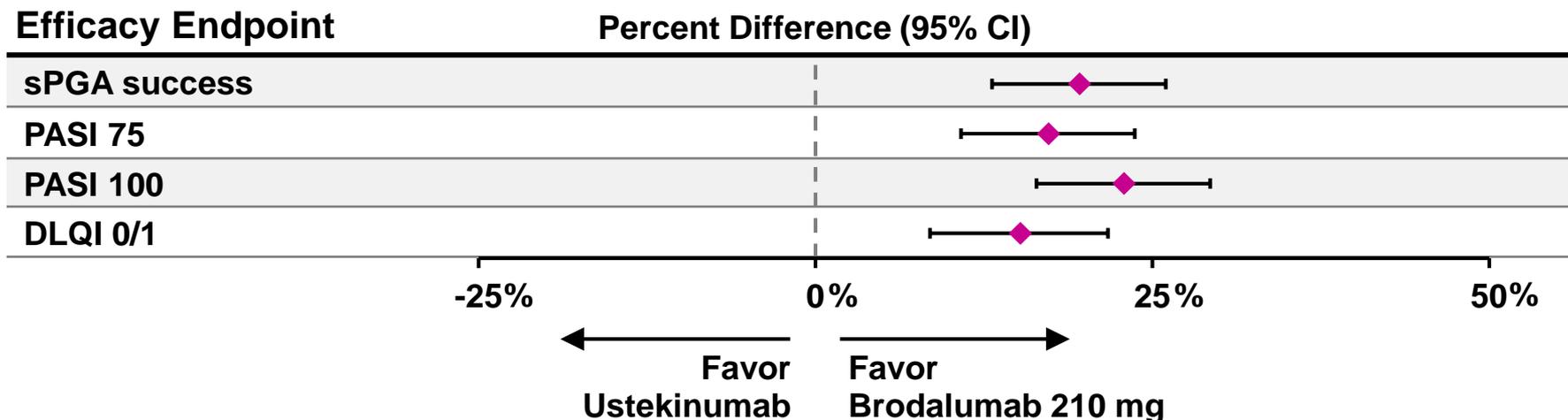
AMAGINE-3, N = 1881/1656

TOTAL: 4548/4065

TOTAL Enrolled/Completed = 5679/5089

Benefit Risk Summary Plot

Psoriasis Studies, Week 52



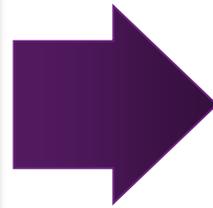
Role of Brodalumab in Current Psoriasis Treatment

Plaque psoriasis is incompletely treated with current therapies

- ▶ Incomplete clearance
- ▶ Loss of effectiveness over time
- ▶ Available agents not effective for every patient

Importance of Disease Clearance

DAY 0



Week 12



Agenda

Medical Landscape	Mark Lebwohl, MD Professor and Chairman Kimberly and Eric J. Waldman Department of Dermatology Icahn School of Medicine at Mount Sinai
Efficacy	RK Pillai, PhD Vice President, Head of Dermatology Development, Valeant
Safety	Robert Israel, MD Vice President, Clinical and Medical Affairs, Valeant
Suicidal Ideation & Behavior	Lauren B. Marangell, MD Psychiatrist and President Brain Health Consultants
IL-17 Signaling & Safety	James B. Trager, PhD Vice President, Research, Valeant
Risk Management	Tage Ramakrishna, MD Chief Medical Officer President of Research and Development, Quality, Valeant
Benefit-Risk	Kim Papp, MD, PhD, FRCPC President, Probitry Medical Research
Conclusion	Tage Ramakrishna, MD

Do we need more psoriasis therapies?

Mark Lebwohl, MD

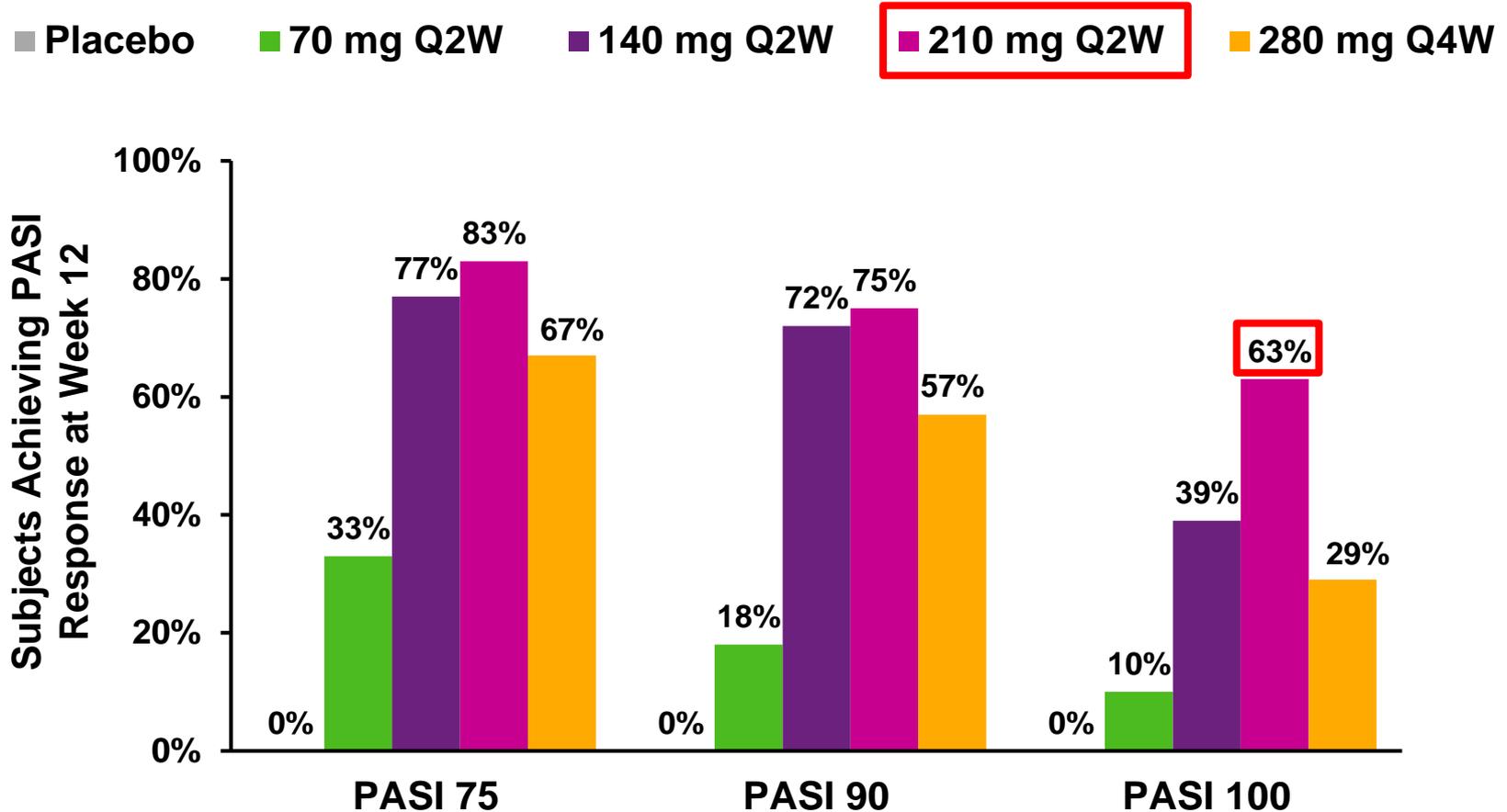
Professor And Chairman

Kimberly and Eric J. Waldman Department of Dermatology

Icahn School of Medicine at Mount Sinai



PASI Response at Week 12







PASI 100













Risk of Myocardial Infarction in Patients with Psoriasis

- **Age 30, Severe Psoriasis**
- **HR: 3.10**

Gelfand JM, Neimann AL, Shin DB, Wang X, Margolis DJ, Troxel AB.
JAMA 2006;296:1735-41

Risk of Depression, Anxiety, and Suicidality in Patients with Psoriasis: a Population-based Cohort Study

	Hazard Ratios (95% CI)
Depression	1.39 (1.37, 1.41)
Anxiety	1.31 (1.29, 1.34)
Suicidality	1.44 (1.32, 1.57)

- In UK >10,400 diagnoses of depression, 7100 diagnoses of anxiety, and 350 diagnoses of suicidality attributable to psoriasis

Psoriasis, Cold Sores Most Stigmatized Skin Disorders: Survey

Results show how misunderstood the conditions are, researchers say



By **Maureen Salamon**

HealthDay Reporter

FRIDAY, Oct. 9, 2015 (HealthDay News) -- Psoriasis and cold sores top the list of stigmatized skin conditions, a new survey indicates, but experts say much of the ill will directed at sufferers is misguided.

Surveying 56 people, Boston researchers found that nearly 61 percent wrongly thought psoriasis -- which produces widespread, scaly red skin lesions -- looked contagious, and about nine in 10 said they would pity a person who had it. About four in 10 said herpes simplex, or cold sore, is the most bothersome skin condition.

"We knew from other studies that psoriasis seemed to be more stigmatizing than other skin diseases, [and] we did this study to try to find out why," said study author Dr. Alexa Kimball, a dermatology professor at Harvard Medical School.

"We suspected that the fact that it looked infectious could be part of the reason people reacted strongly to it, but we didn't expect that reaction to be as strong as it was," Kimball said. "This result ... provides an obvious opportunity to educate the public about the fact that

Disease-induced Level of Shame in Patients with Acne, Psoriasis and Syphilis

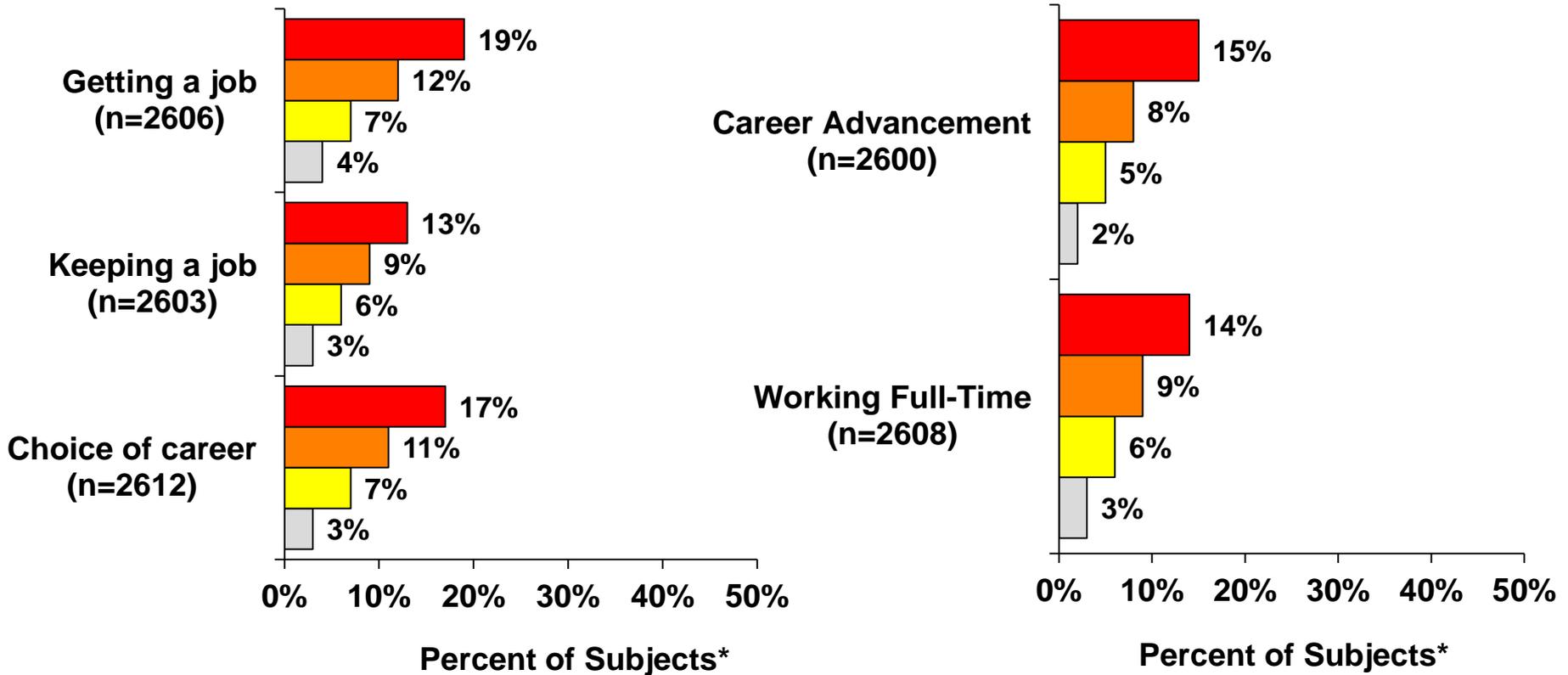
- **Syphilis > psoriasis > acne**
- **Psoriasis is in the top 10 most embarrassing diseases**

Patient Perspectives in the Management of Psoriasis: Results from the Population-based Multinational Assessment of Psoriasis and Psoriatic Arthritis Survey

- **139,948 households called**
- **3426 patients surveyed**

PsO Interferes with Employment

■ > 10% BSA
 ■ 4-10% BSA
 ■ 1-3% BSA
 ■ < 1% BSA

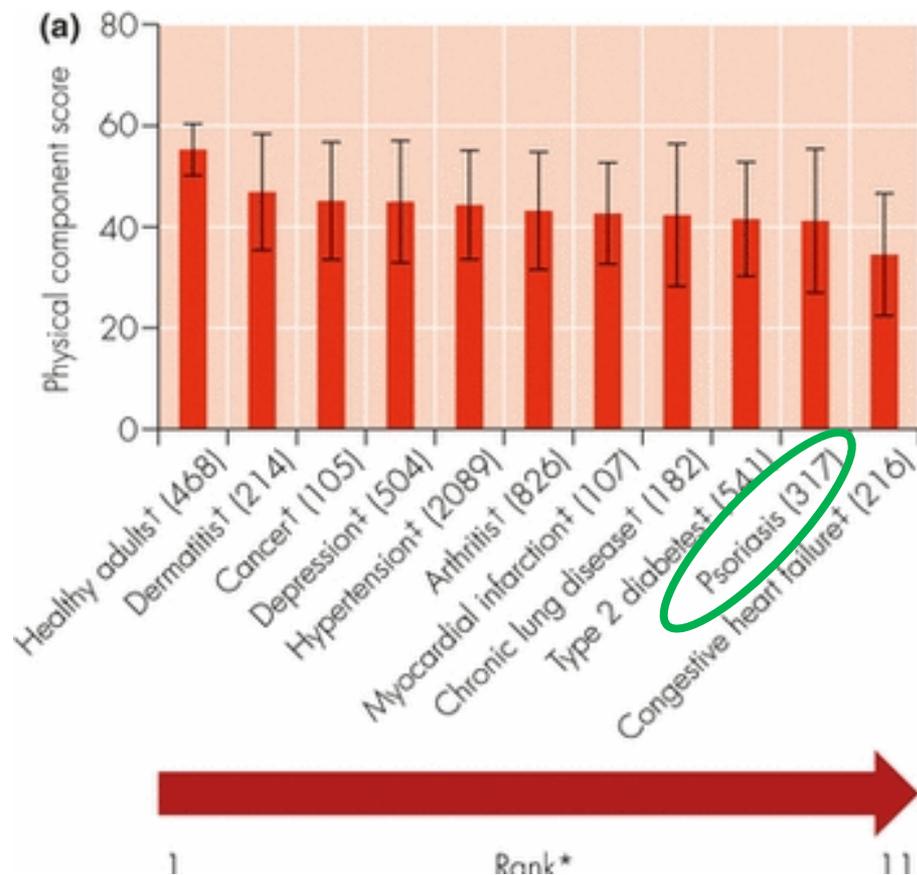


*Percent of Subjects with PsO/PsA responding "very much" or "a lot"

Work Productivity Data

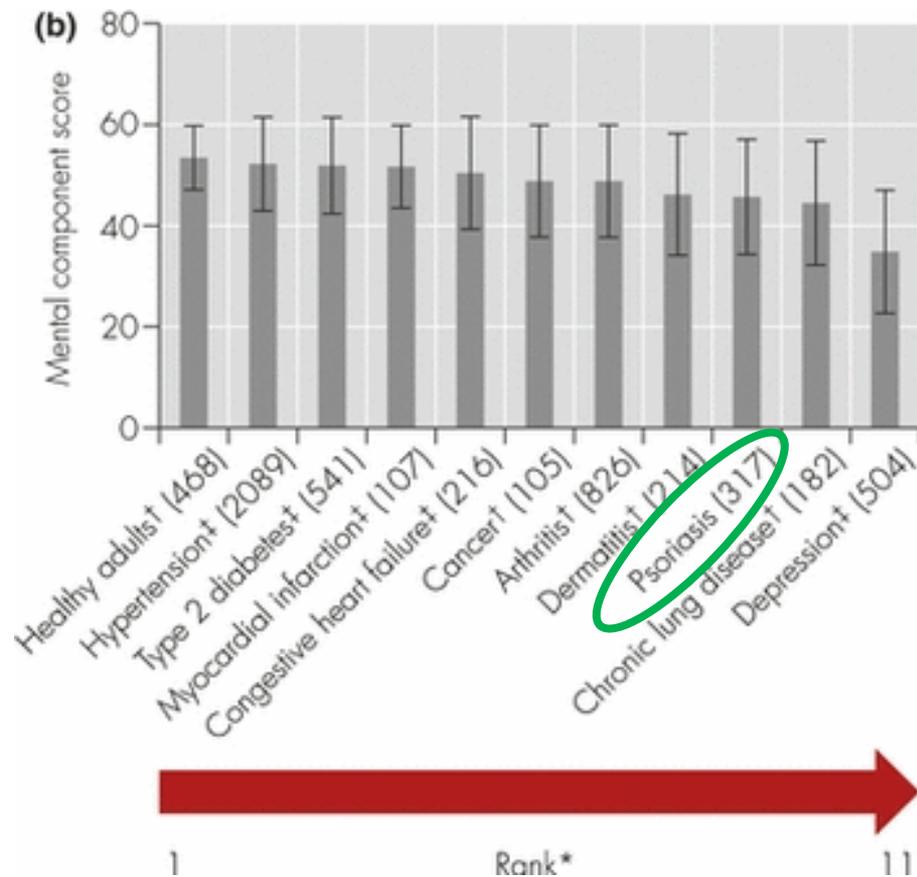
- **Lewis-Beck et al 2014: WPAI results from 199 psoriasis subjects with at least 10% BSA affected (based on NHWS)**
 - ▶ Missed work due to psoriasis: 25%
 - ▶ Decreased productivity: 65%
 - ▶ Activity impairment: 72.3%

A Framework for Improving the Quality of Care for People with Psoriasis – Physical Component Score



Journal of the European Academy of Dermatology and Venereology pages 1-16, 21 JUN 2012 DOI: 10.1111/j.1468-3083.2012.04576.x;
<http://onlinelibrary.wiley.com/doi/10.1111/j.1468-3083.2012.04576.x/full#f2>

A Framework for Improving the Quality of Care for People with Psoriasis – Mental Component Score



Journal of the European Academy of Dermatology and Venereology pages 1-16, 21 JUN 2012 DOI: 10.1111/j.1468-3083.2012.04576.x;
<http://onlinelibrary.wiley.com/doi/10.1111/j.1468-3083.2012.04576.x/full#f2>

Drawbacks of Non-biologic Psoriasis Therapies

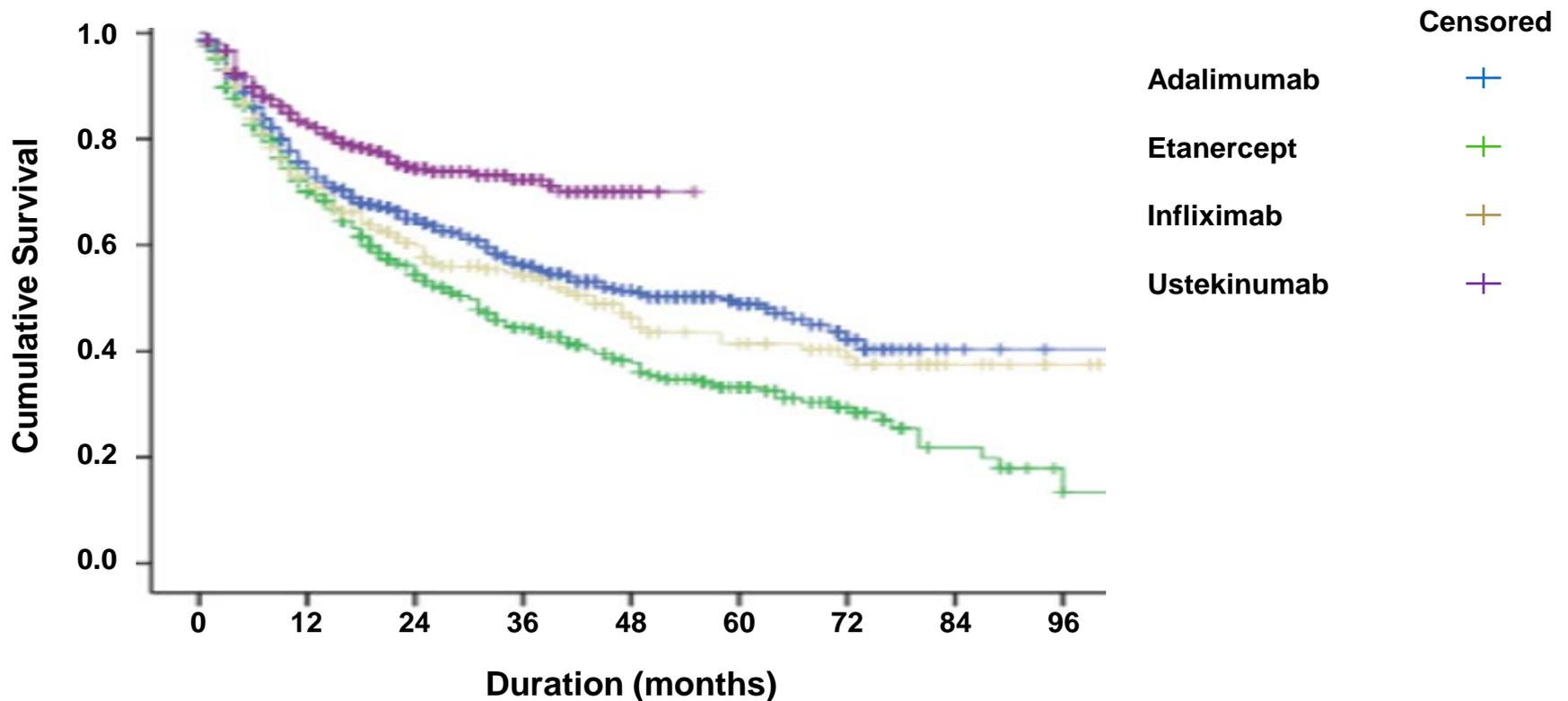
UVB	Visits 3 times/week, burns
PUVA	Visits 3 times/week, melanoma/SCC, burns
Acitretin	Teratogenic, modest efficacy
Methotrexate	Bone marrow toxicity, hepatotoxicity
Cyclosporine	Nephrotoxicity, hypertension
Apremilast	Diarrhea, weight loss, modest efficacy

Drawbacks of Biologic Therapies

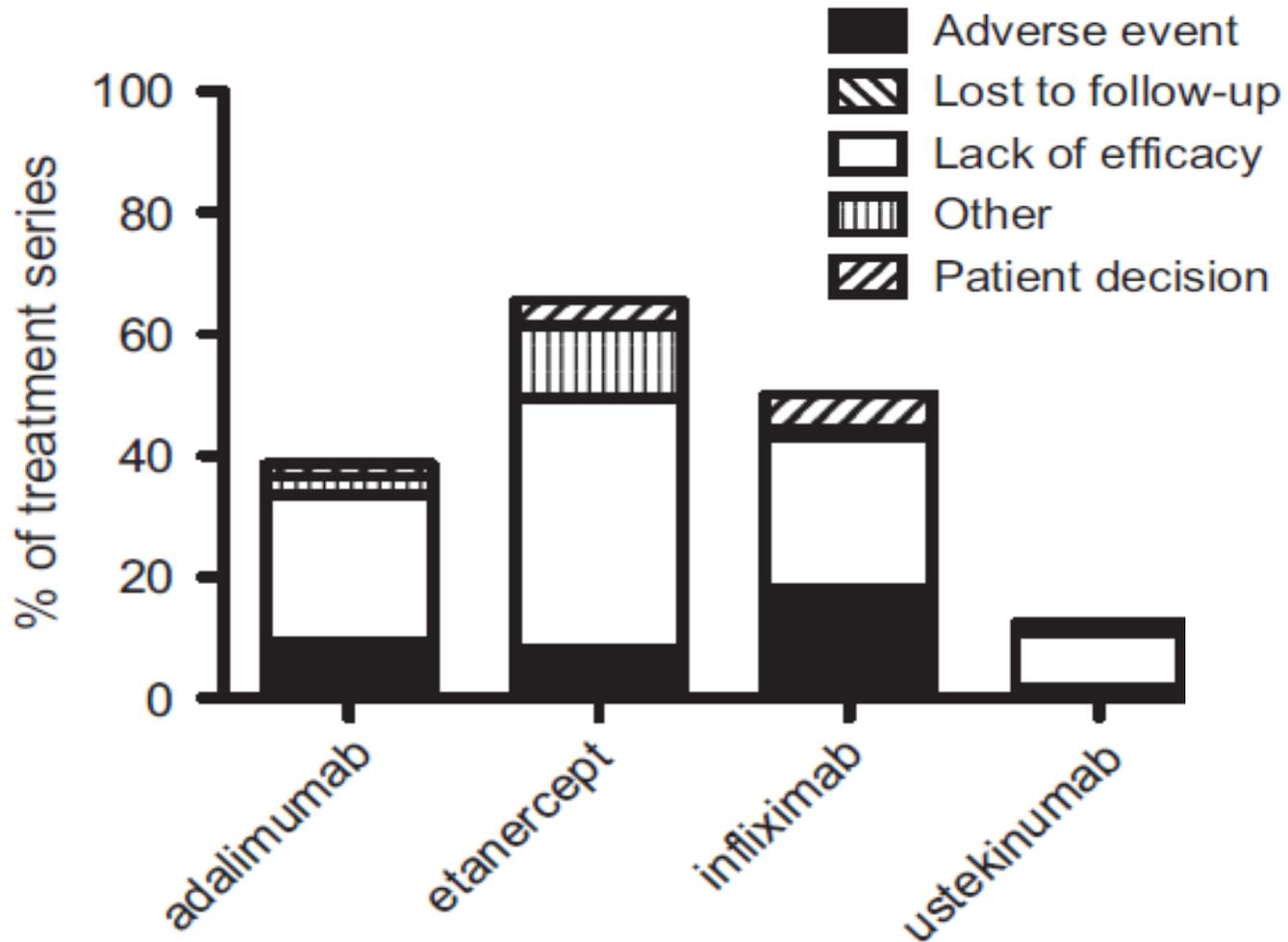
- **Cost**
- **Administered by injection**
- **Heart failure**
- **Connective tissue disease**
- **Demyelinating diseases**
- **Infection**
- **Malignancy**
- **Loss of efficacy over time**

Differential Drug Survival of Biologic Therapies for the Treatment of Psoriasis: A Prospective Observational Cohort Study from the British Association of Dermatologists Biologic Interventions Register (BADBIR)

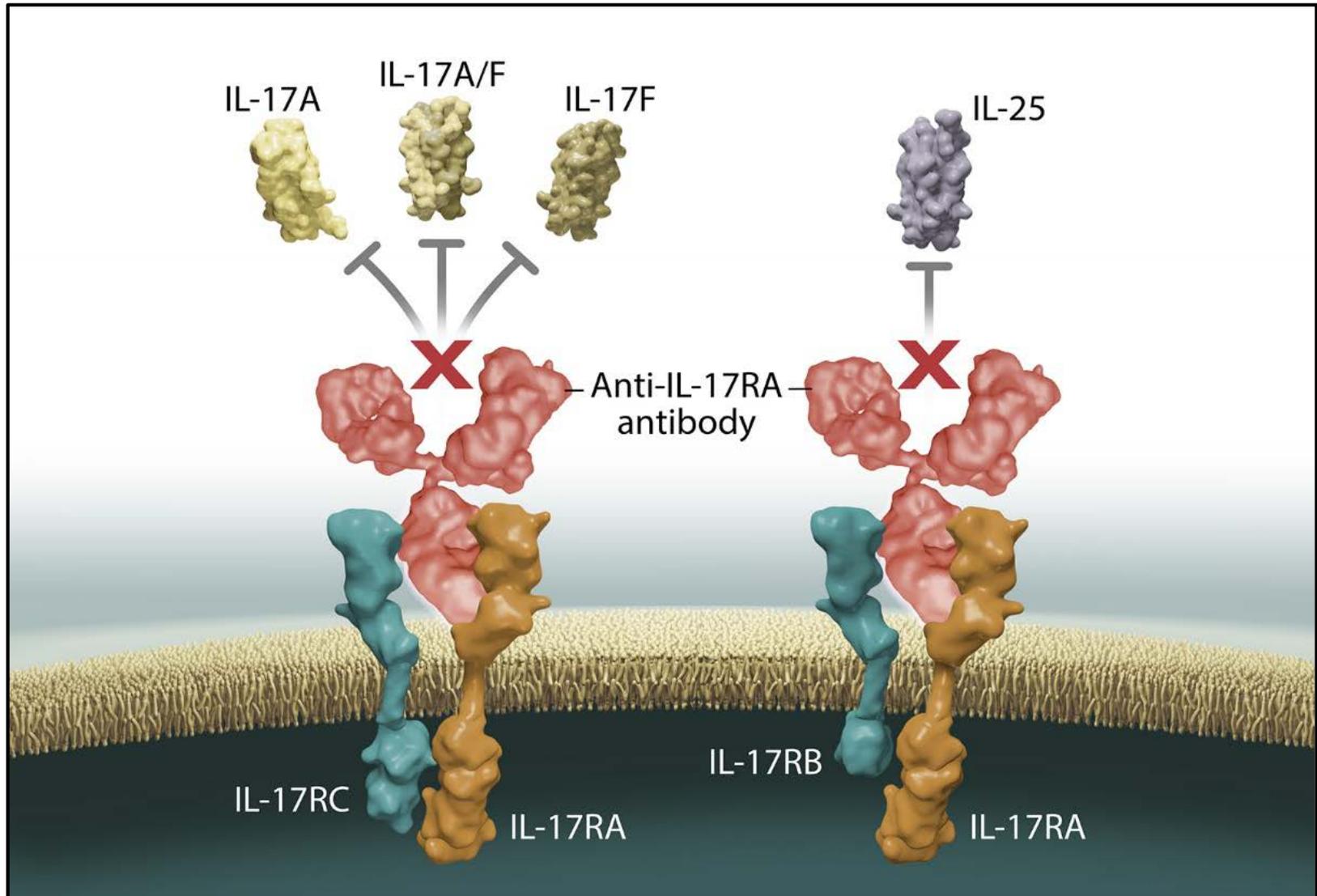
KM Survival Curve for all Treatment Sequences from DERMBIO Database



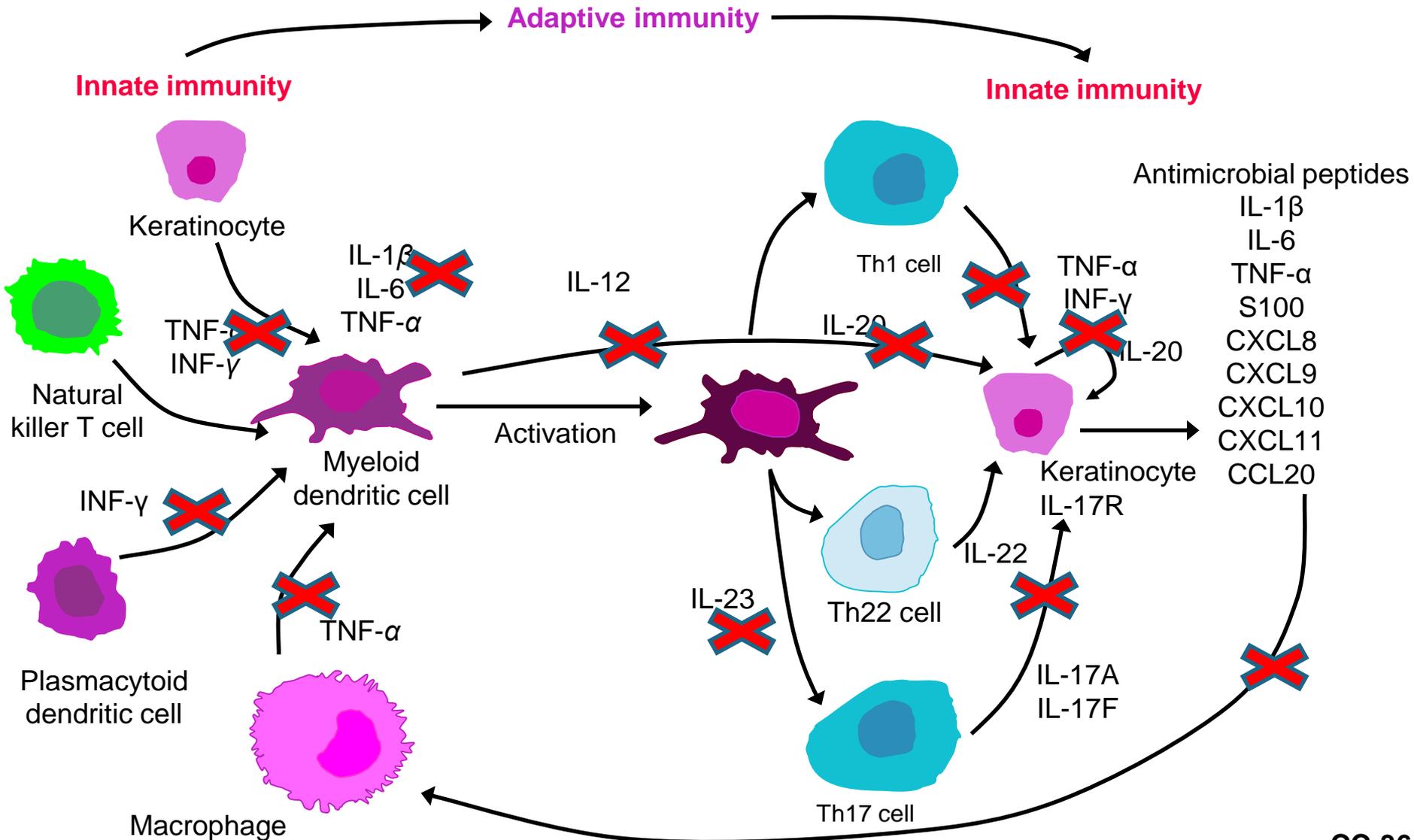
Reasons for Termination of Biological Treatment in all Treatment Series in Patients Previously Exposed to a Biologic



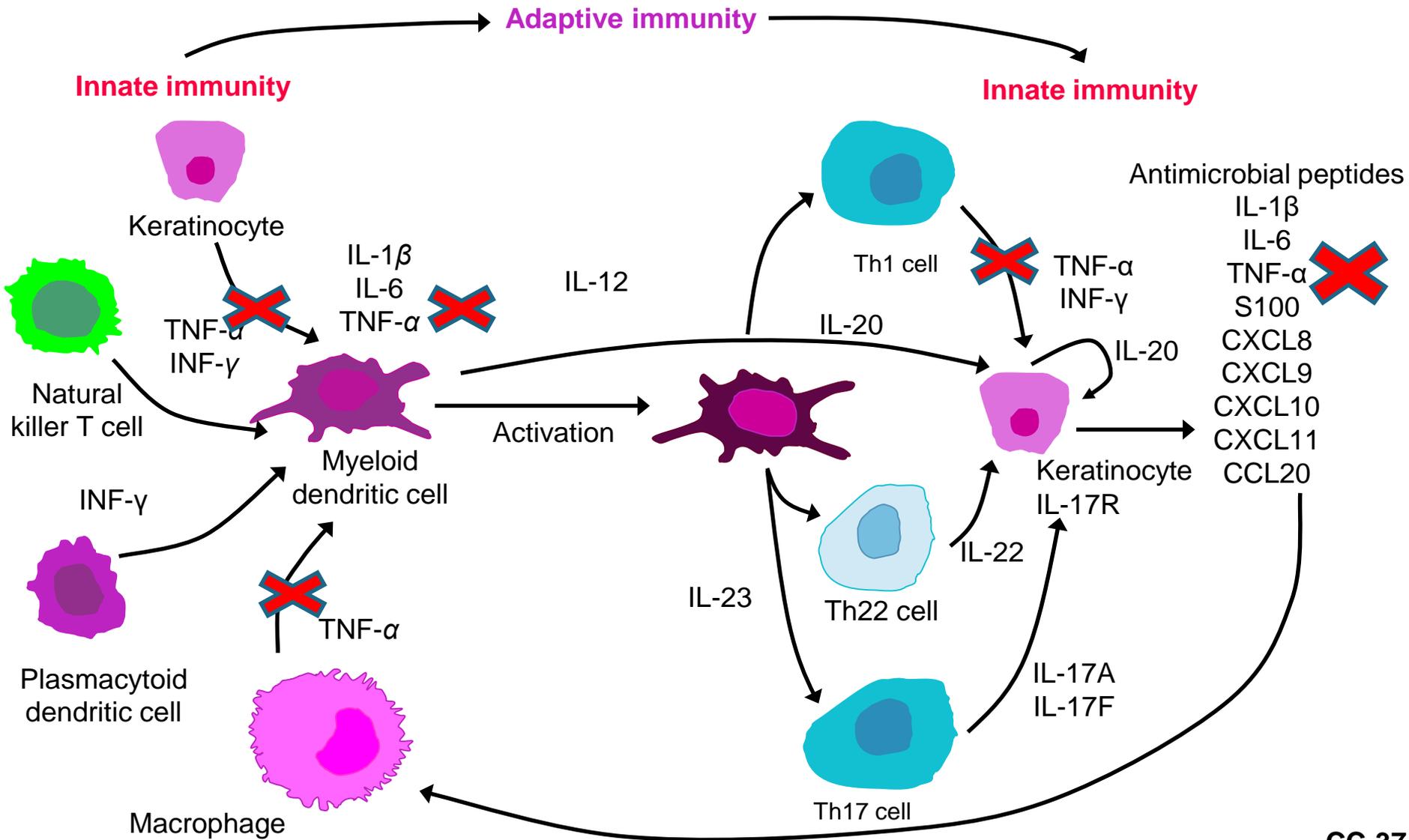
Brodalumab – Anti-IL-17RA antibody



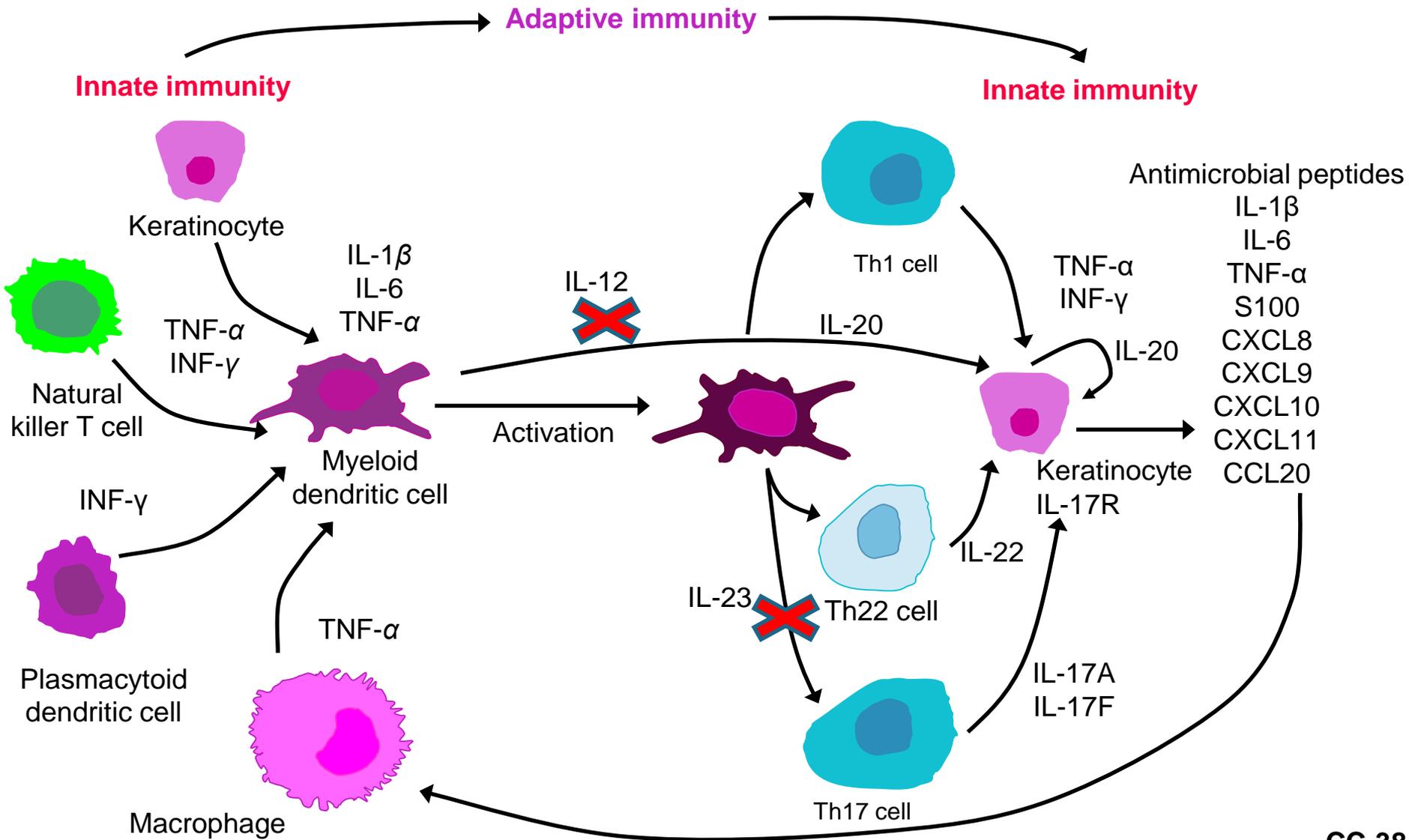
Mechanism of Cyclosporine



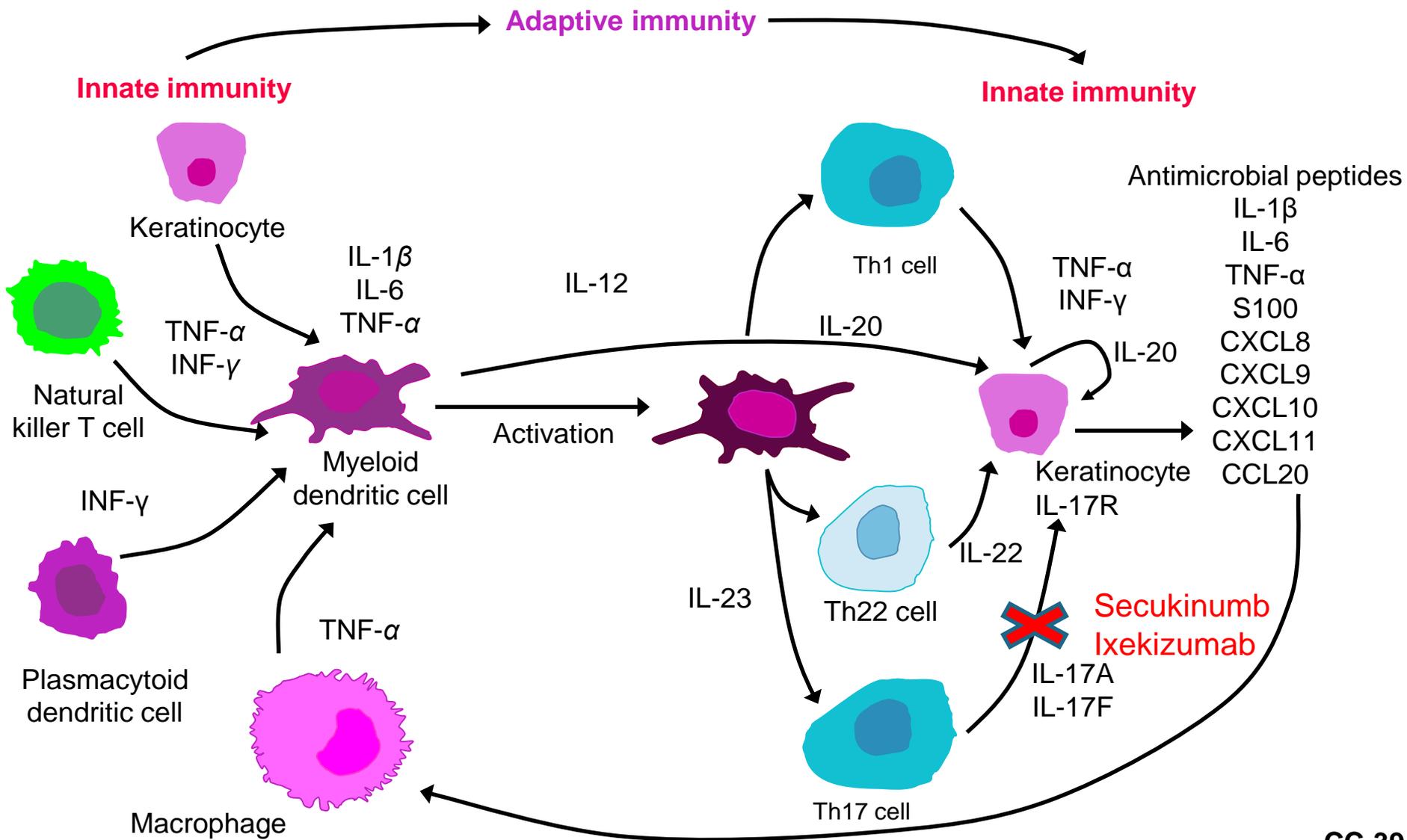
Mechanism of TNF Blockers



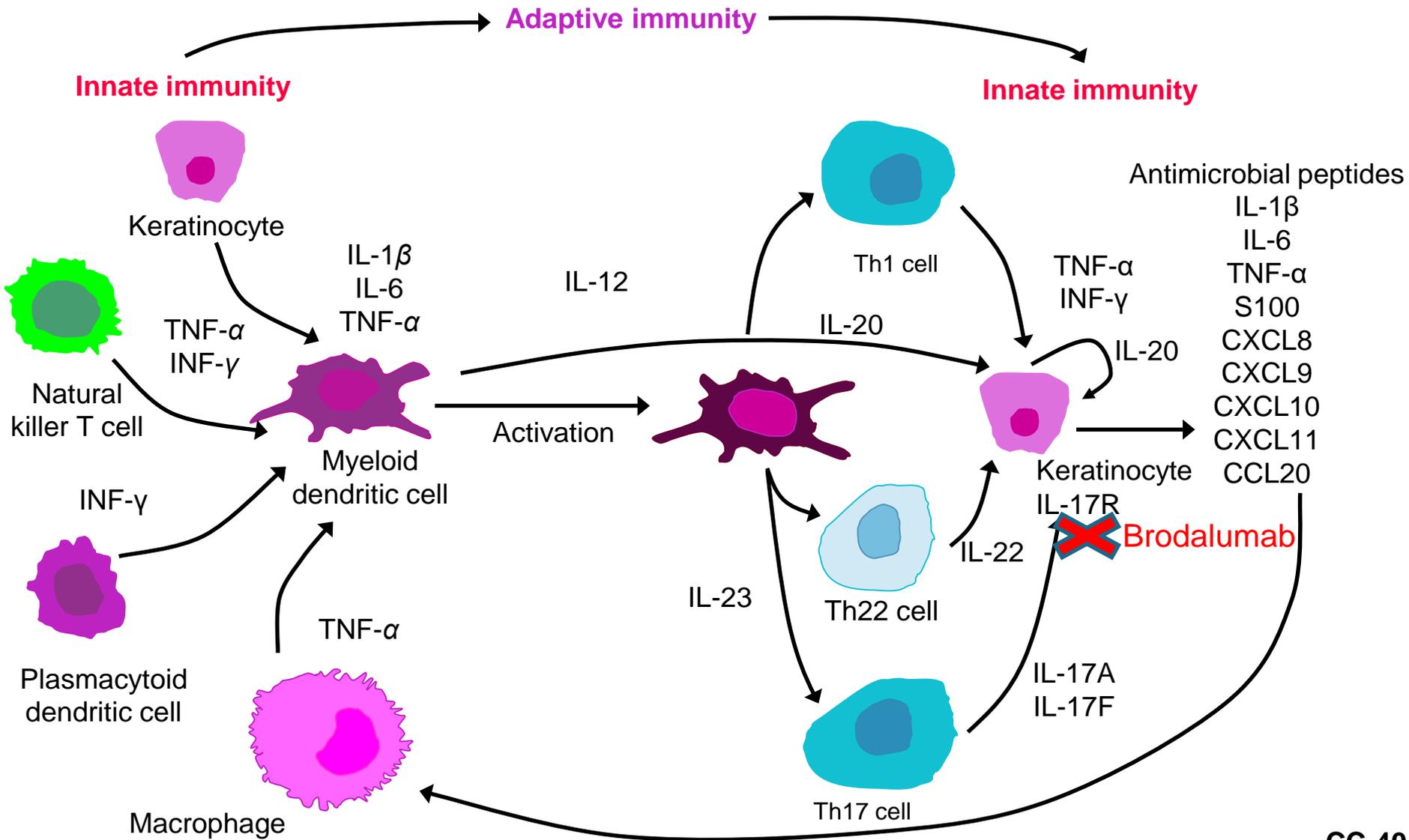
Mechanism of Ustekinumab



Mechanism of Secukinumab & Ixekizumab



Mechanism of Brodalumab



IL-17 Deficiency

- **Immunity to infection in IL-17-deficient mice and humans¹**
- **Chronic mucocutaneous candidiasis in humans with inborn errors of interleukin-17 immunity²**

¹Cypowyj S, Picard C, Maródi L, et al *Eur J Immunol*. 2012;42:2246-2254.

²Puel A, Cypowyj S, Bustamante J, et al. *Science*. 2011;332(6025):65-68.

Inherited IL-17RC Deficiency

- **Inherited IL-17RC deficiency in patients with chronic mucocutaneous candidiasis**

PASI 100



Week 4 (PASI75)

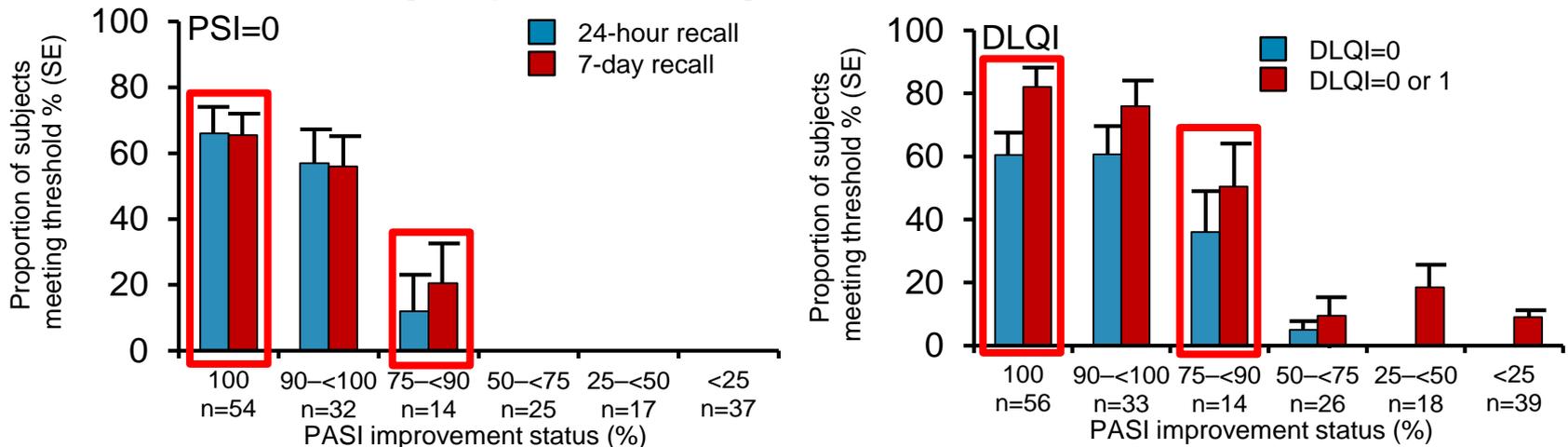


Incremental Difference in Improvements of Patient Reported Outcomes (PRO) Measures Between Psoriasis Area and Severity Index (PASI) 100 and 75 Groups

- **Data from brodalumab Phase II trial**

- ▶ Evaluated the Psoriasis Symptom Inventory (8 item, psoriasis-specific PRO instrument):
 - Itch, stinging, scaling, flaking, burning, pain, redness, cracking
 - Each item scored on a scale of 0 (not at all severe) to 4 (very severe) with the total score (sum of the 8 items) ranging from 0 (best) to 32 (worst)
 - A total PSI=0 reflects resolution of psoriasis symptoms
 - Recall over 24 hours or 7 days
- ▶ Also evaluated DLQI

Percentage of patients meeting PSI and DLQI thresholds at Week 12







As your patient, I had received numerous medications over the past 20 years or so with mixed results. The best medicine I had ever taken for my psoriasis (and psoriatic arthritis) was Brodalumab. I was 100% clear from skin plaques and had never felt happier with regard to my body and my quality of life. I had NO suicidal ideation and no depressive symptoms whatsoever during the entire trial which was several years. In fact, I was significantly saddened and worried about the abrupt discontinuation of this trial and the potential resurgence of my symptoms. I have since been placed on other FDA approved medicines with not the same clinical benefits.

I believe it was a huge mistake to discontinue such an efficacious treatment and I feel that the dermatological patients of the world have been deprived of the most effective treatment I have ever known. My hope is that Brodalumab is reintroduced to patients as I am confident this medicine will improve the medical and psychological health of innumerable patients in the future.

Alec L. Miller, PsyD, Clinical Professor of Psychiatry and Behavioral Sciences
Montefiore Medical Center/Albert Einstein College of Medicine

Efficacy

RK Pillai, PhD

Vice President

Head of Dermatology Development

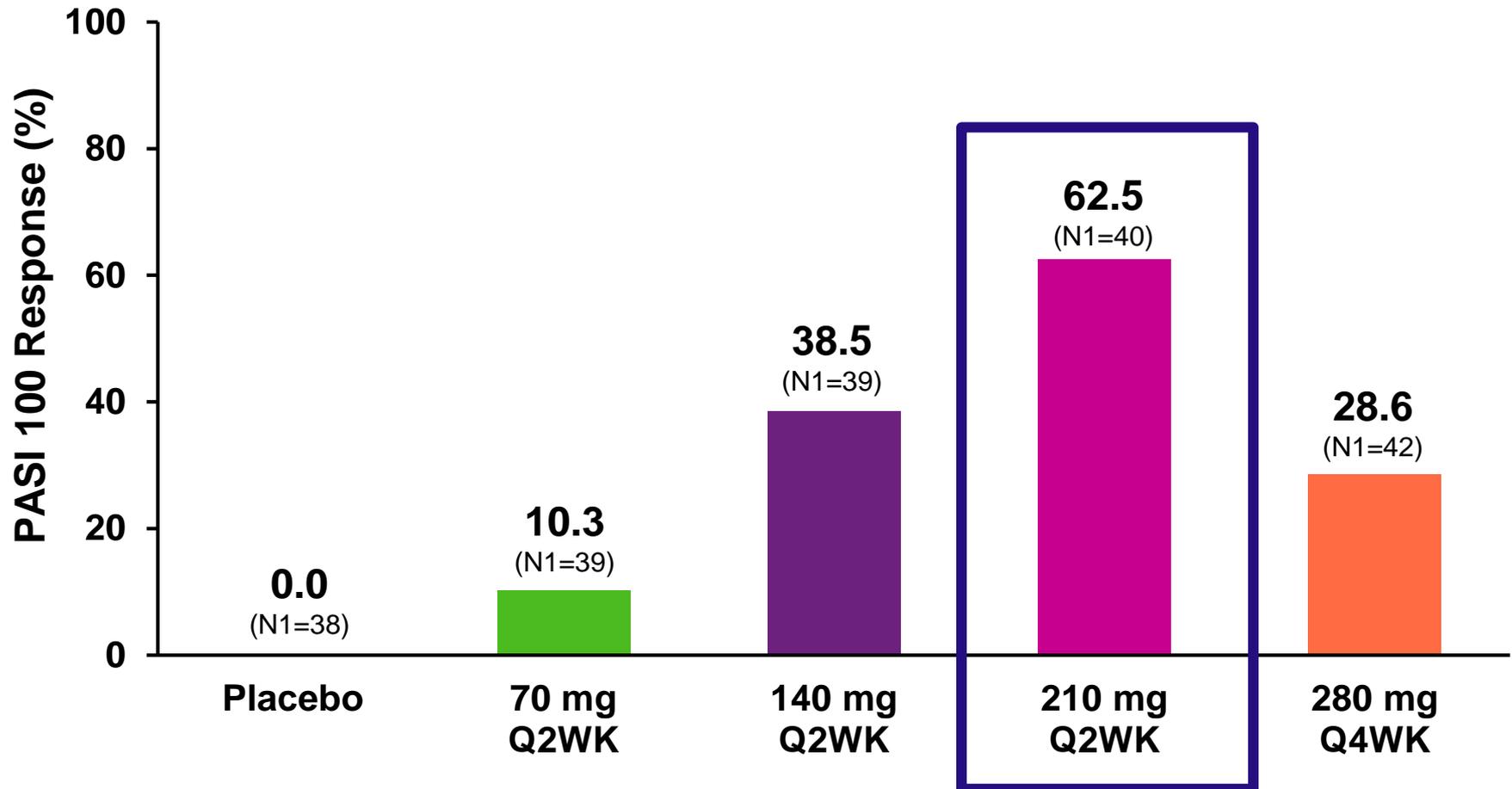
Valeant

Brodalumab Efficacy in Psoriasis

- **Efficacy in moderate to severe psoriasis has been established in four safety and efficacy studies**
- **Key results from brodalumab 210 mg Q2W**
 - ▶ Rapid onset of action as early as two weeks
 - ▶ More than 50% of patients achieved complete clearance (PASI 100) within a year
 - ▶ Confirmed its superiority over ustekinumab

Brodalumab: Phase 2 Study Results

PASI 100 (NRI) Week 12



NRI: Non responder imputation

Brodalumab Phase 3 Studies (Psoriasis)

- Large, robust, multicenter, well-characterized, placebo and comparator controlled studies
- Over 4300 patients evaluated during Phase 3

AMAGINE-1	AMAGINE-2	AMAGINE-3
661 patients	1831 patients	1881 patients
210 mg Q2W 140 mg Q2W Placebo	210 mg Q2W 140 mg Q2W (Q4W, Q8W) Placebo, Ustekinumab (Stelara®)	
12 Week Placebo controlled	12 Week Placebo and comparator controlled	
12-52 Weeks Withdrawal and retreatment	12-52 Weeks Maintenance and comparator controlled	
>52 Weeks Open Label Long-term extension	>52 Weeks Open Label Long-term extension	

Key Inclusion Criteria

- **Stable moderate-severe plaque psoriasis ≥ 6 months**
- **sPGA (static Physician's Global Assessment) ≥ 3 or moderate disease at screening and at baseline**
- **PASI (Psoriasis Area and Severity Index) ≥ 12 at screening and at baseline**
- **Involved BSA (body surface area) $\geq 10\%$ at screening and at baseline**

Not Specifically Excluded

Patients with history of:

- **Drug/alcohol abuse**
- **Depression**
- **Suicidality or**
- **Other psychiatric conditions**

Key Baseline Characteristics Consistent Across 3 Studies

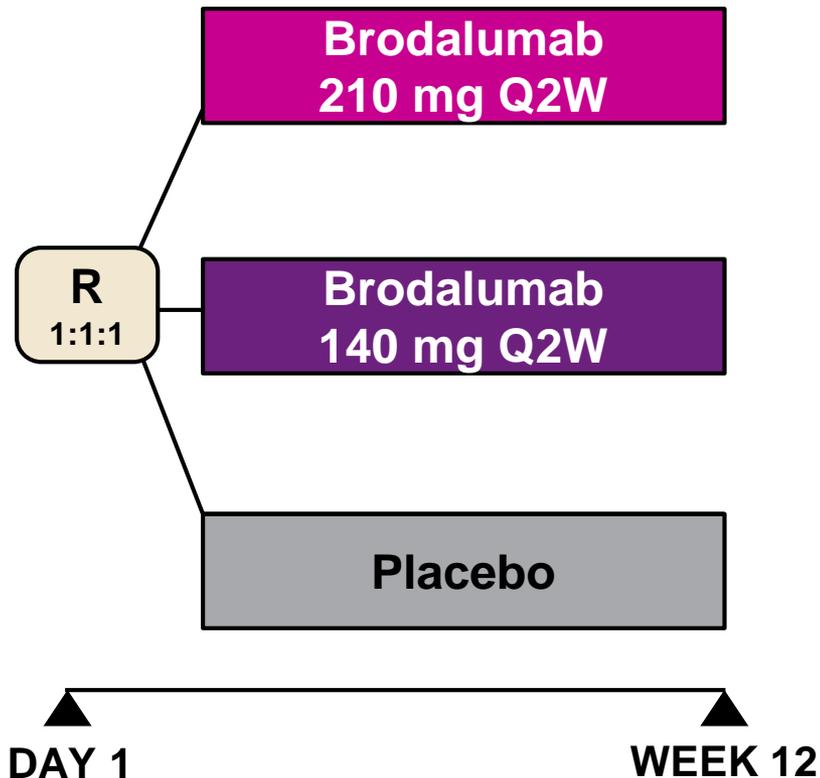
	AMAGINE-1 N=661	AMAGINE-2 N=1831	AMAGINE-3 N=1881
Mean Age (years)	46.3	44.6	44.8
Gender, % Male	73.2	68.7	68.5
Race, % White	90.9	90.2	90.8
Mean % BSA involvement	26.45	26.85	28.26
Mean PASI	19.69	20.31	20.20
% Severe/very severe sPGA (4/5)	44.9	45.7	37.8
Mean DLQI	14.1	14.7	14.5
Mean PSI	19.2	18.8	18.5
Mean disease duration (years)	20.2	18.6	17.7
% Previous biologic experience	46.1*	28.9	26.1

BSA=body surface area, DLQI=Dermatology Life Quality Index, PASI=Psoriasis Area and Severity Index , PSI=Psoriasis Symptom Inventory, sPGA=static Physician's Global Assessment

* AMAGINE-1 did not exclude previous ustekinumab users

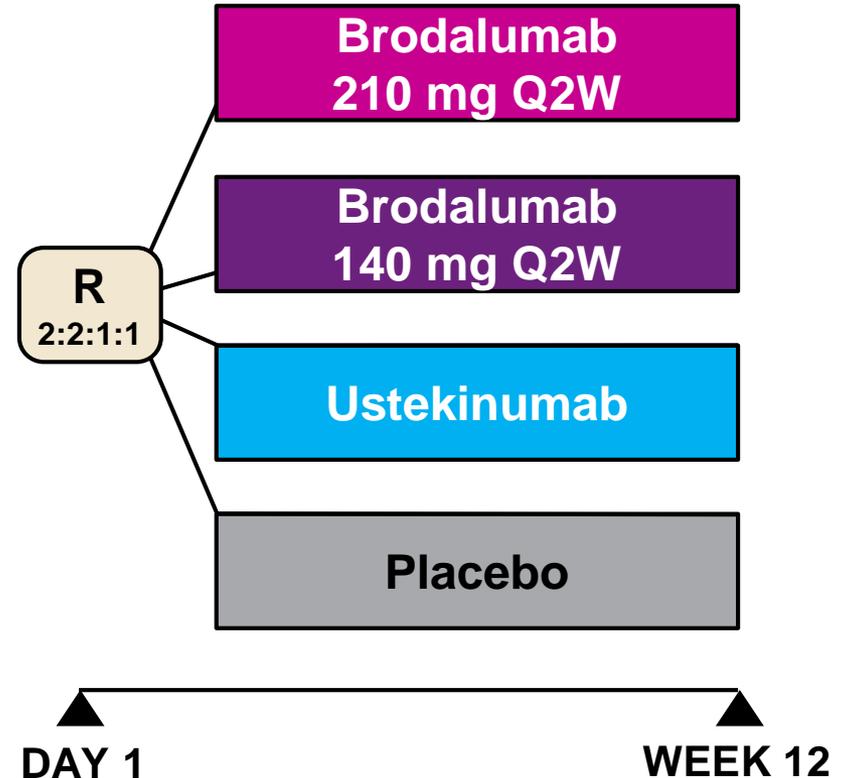
Weeks 0-12: Placebo-Controlled Period

AMAGINE-1
(661 patients)



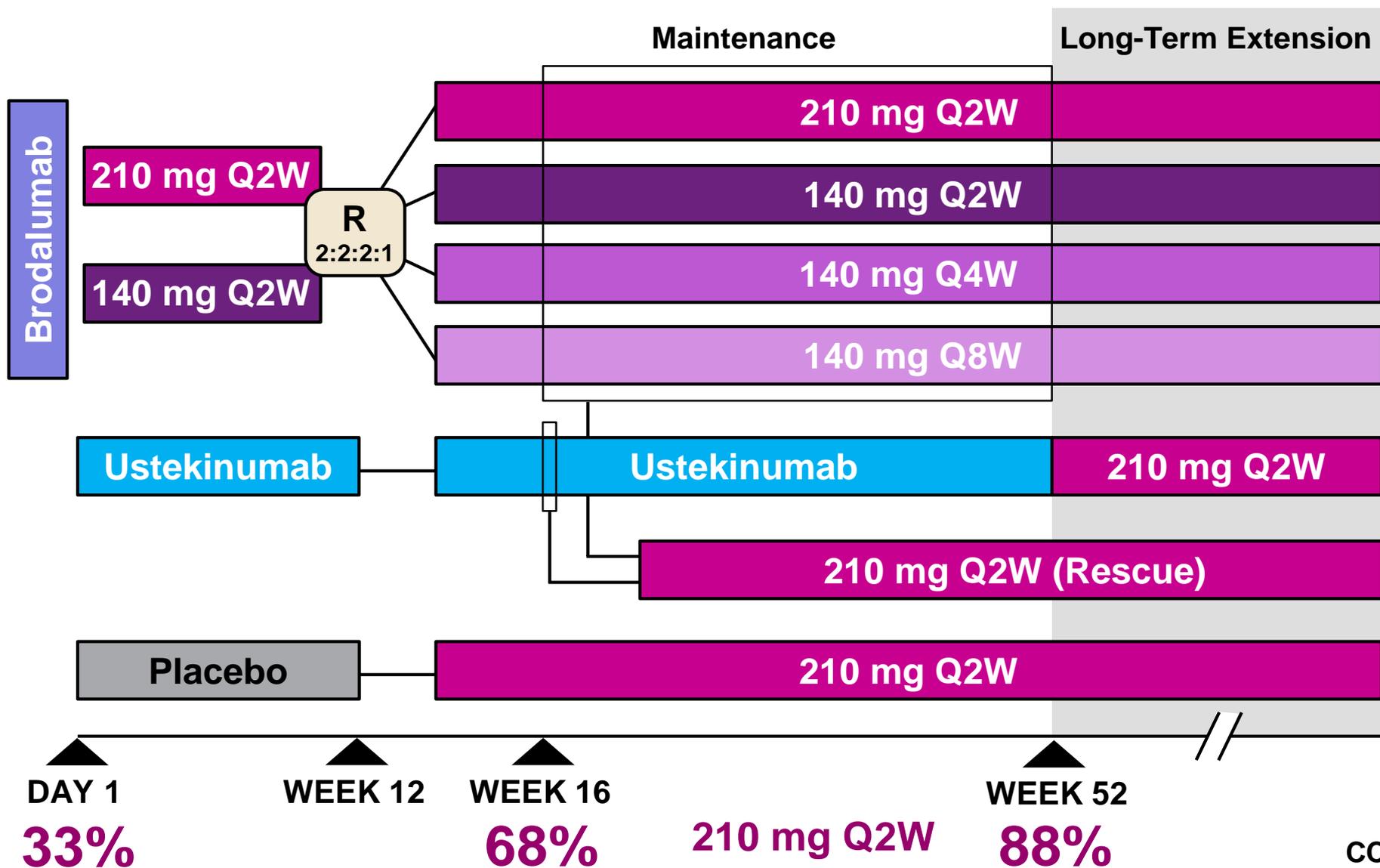
AMAGINE-2
(1831 patients)

AMAGINE-3
(1881 patients)



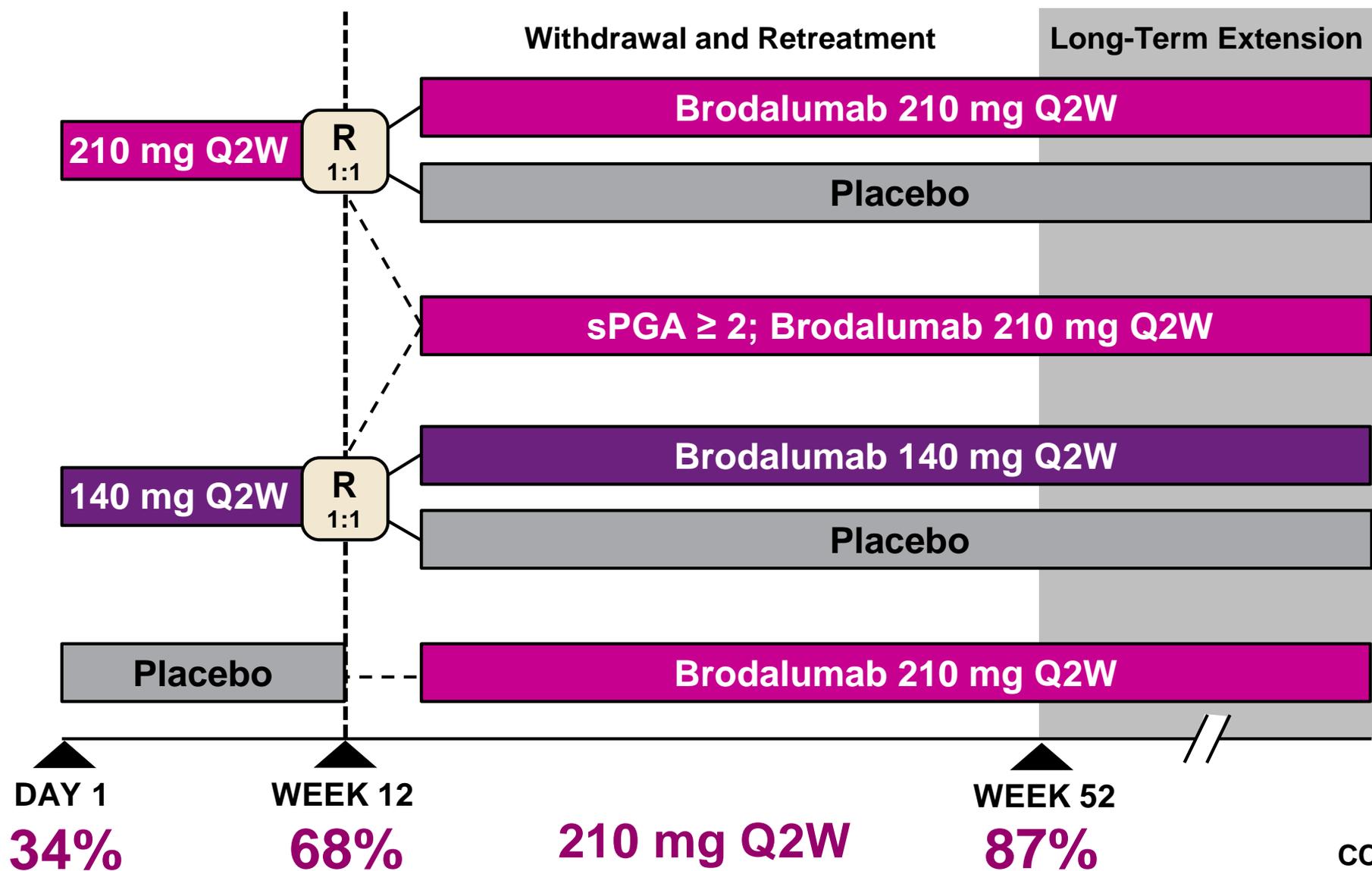
Weeks 12-52 and Long-Term Extension

AMAGINE-2 and AMAGINE-3



Weeks 12-52 and Long-Term Extension

AMAGINE-1



Primary Endpoints

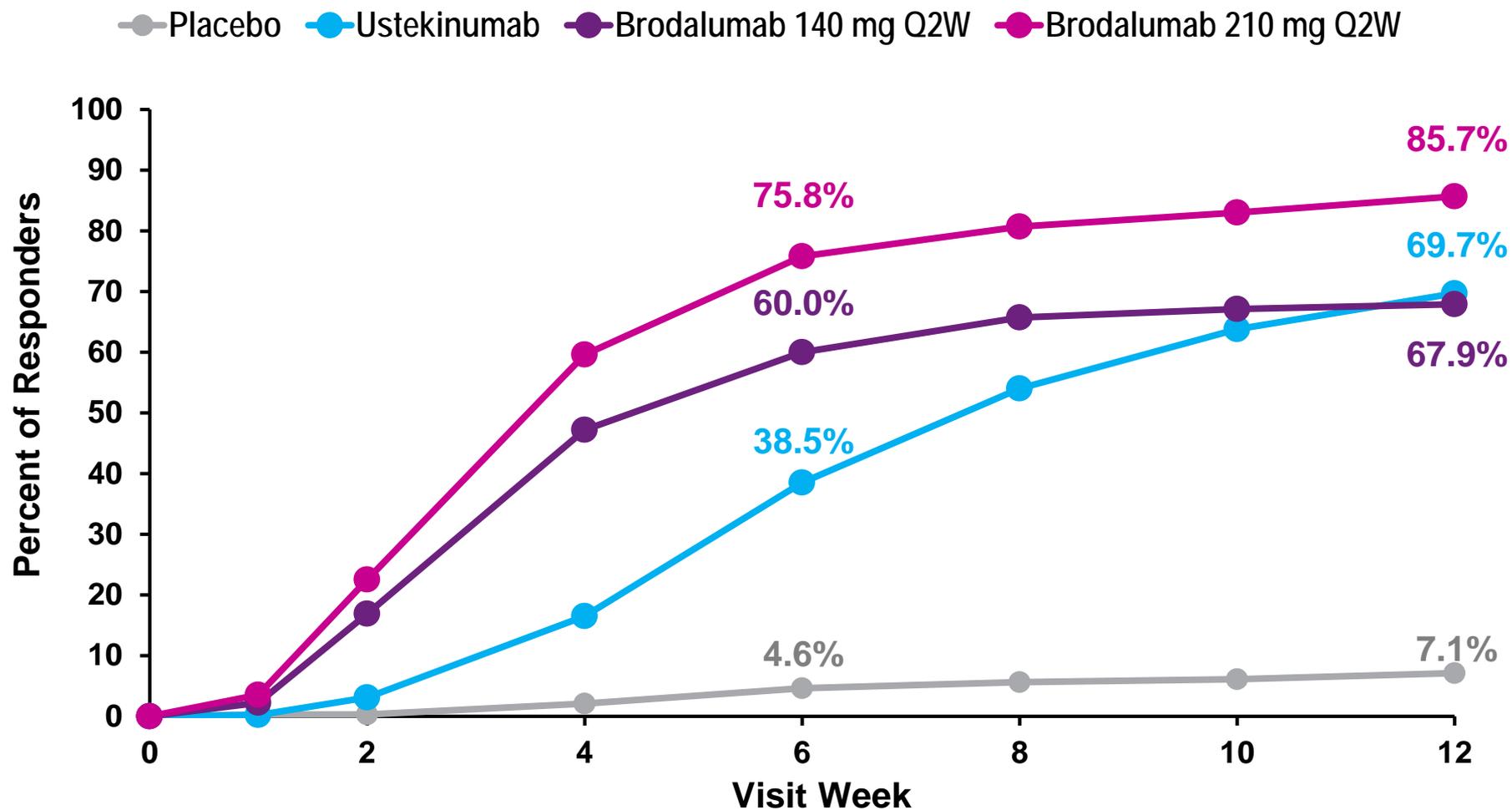
	AMAGINE-1	AMAGINE-2 and AMAGINE-3	
	Brodalumab vs Placebo	Brodalumab vs Placebo	Brodalumab vs Ustekinumab
At 12 Weeks	PASI 75 <ul style="list-style-type: none"> 140 mg Q2W  210 mg Q2W  	PASI 75 <ul style="list-style-type: none"> 140 mg Q2W  210 mg Q2W  	PASI 100 <ul style="list-style-type: none"> 210 mg Q2W  Weight-based* 
	sPGA (0/1) <ul style="list-style-type: none"> 140 mg Q2W  210 mg Q2W  	sPGA (0/1) <ul style="list-style-type: none"> 140 mg Q2W  210 mg Q2W  	

•  = p<0.001

• Weight-based = patients ≤ 100 kg at baseline randomized to 140 mg Q2W or > 100 kg at baseline randomized to 210 mg Q2W.

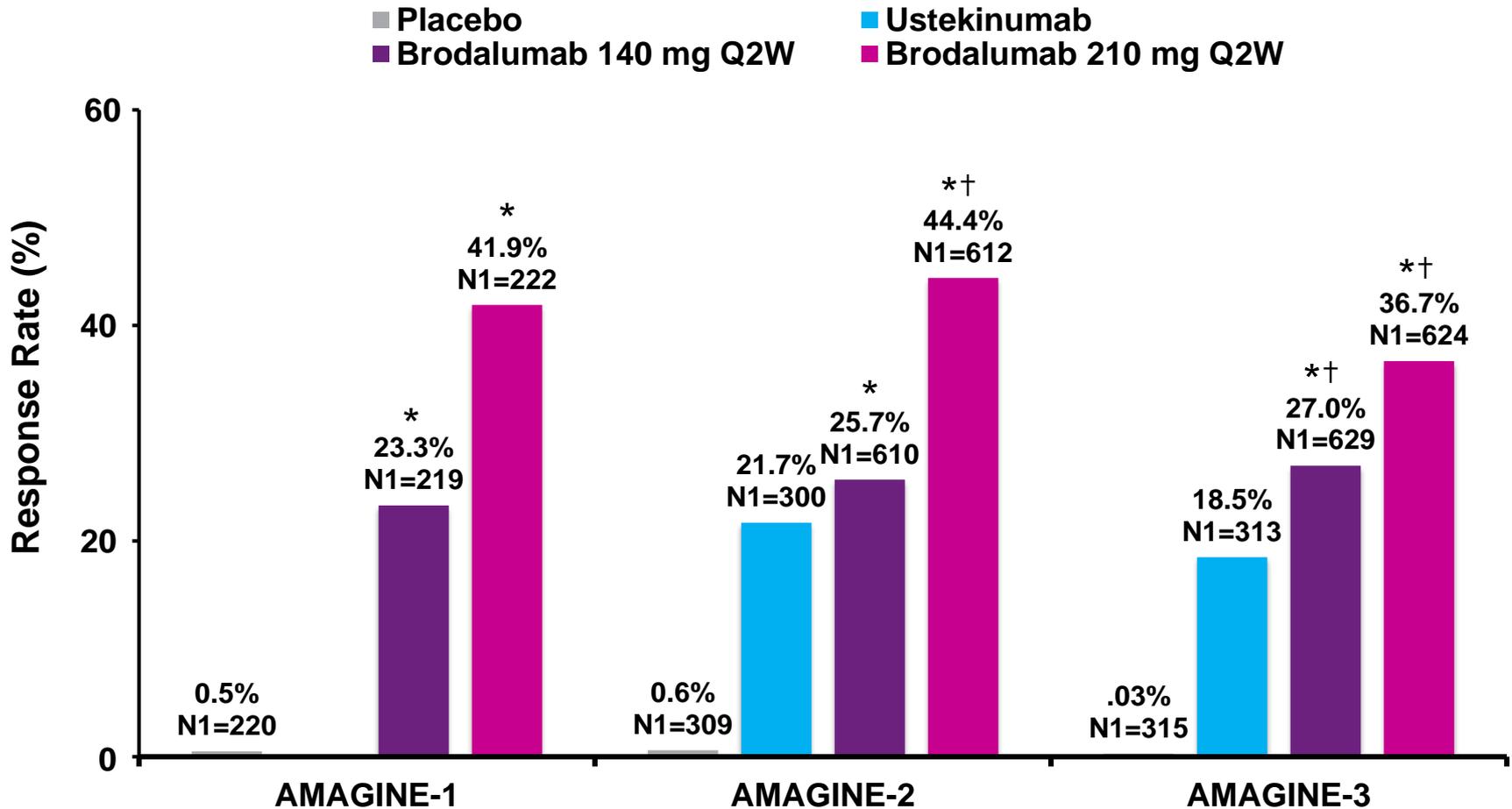
Brodalumab Has Rapid Onset of Action

PASI 75 (NRI): Week 12



AMAGINE-2 and AMAGINE-3

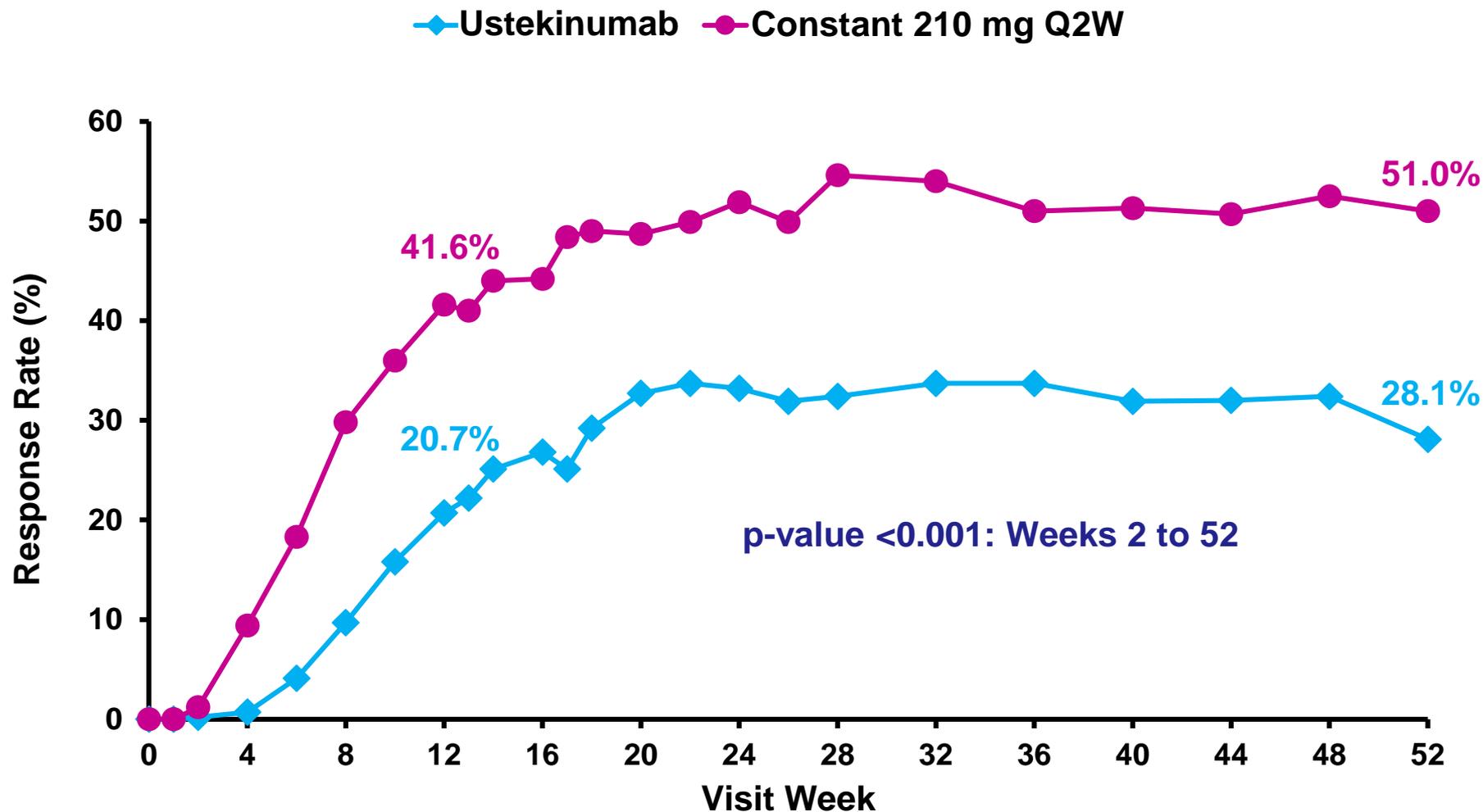
PASI 100 (NRI): Brodalumab 210 mg Q2W Superior to Ustekinumab and Placebo (Week 12)



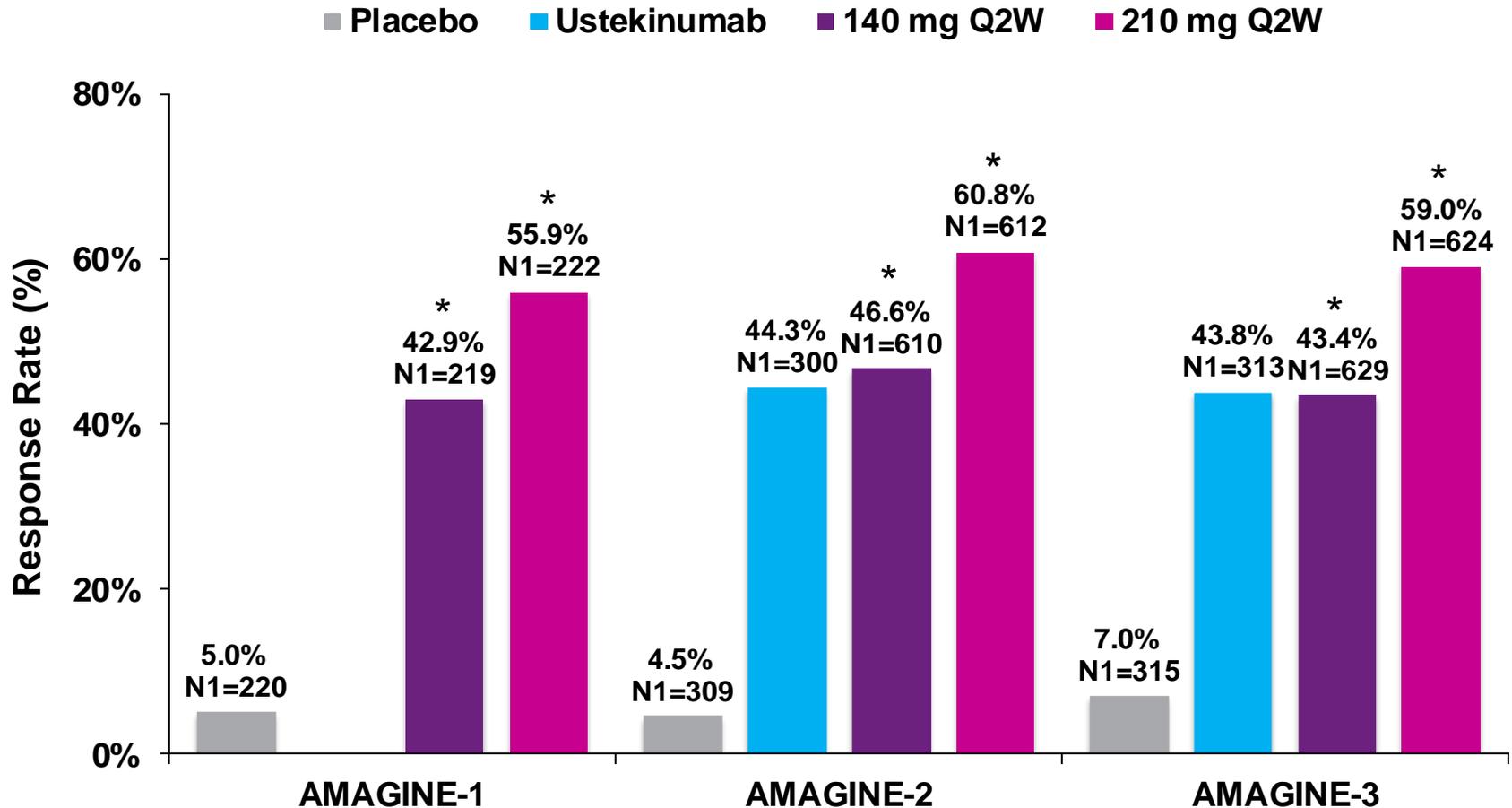
* p<0.001 vs Placebo

†p<0.001 vs Ustekinumab

PASI 100 (NRI): Brodalumab 210 Q2W Superior to Ustekinumab



DLQI (Dermatology Life Quality Index) Higher Patient Satisfaction with Brodalumab 210 mg Q2W

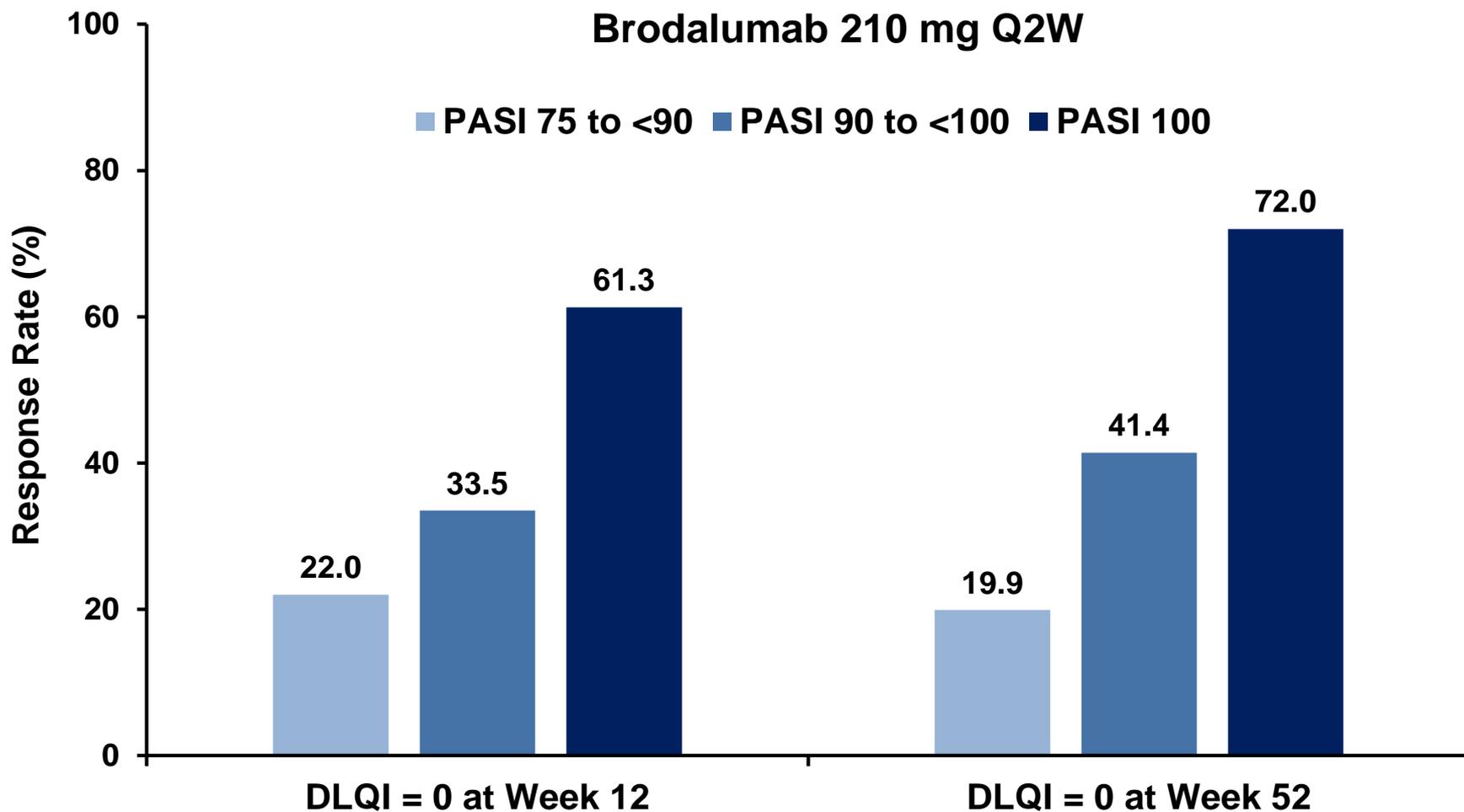


DLQI response = score 0/1

* p<0.001 vs Placebo

Week 12

Higher Patient Satisfaction with Complete Clearance (PASI 100)



AMAGINE-1, AMAGINE-2, and AMAGINE-3

Efficacy Conclusions: Brodalumab 210 mg Q2W

- **Efficacy in moderate to severe psoriasis has been established in over 4300 patients**
- **Rapid onset of action as early as two weeks**
- **Confirmed its superiority over ustekinumab**
- **High level of patient satisfaction**
- **More than 50% of patients achieved complete clearance (PASI 100) within a year**

Safety

Robert Israel, MD

Vice President, Clinical and Medical Affairs
Valeant Pharmaceuticals

Patient Exposure to Brodalumab 210 mg

Phase 2 and Phase 3 Psoriasis Studies

	210 mg	All Doses
Dosing (n)		
≥1 Dose	4114 (92%)	4464
Duration (n)		
≥3 Months	3741	4026
≥12 Months	3135	3515
≥24 Months	1372	2211
Exposure (PY)	6562.7 (76%)	8604.7

PY = Patient Year

Treatment Groups for Safety Reporting

	Placebo	Ustekinumab	Brodalumab		
			Constant 140 mg Q2W	Constant 210 mg Q2W	All Doses*
12-Week Period	N=879	N=613	N=1491	N=1496	N=3066
52-Week Period		N=613	N=280	N=1335	N=4019
			Overall 140 mg Q2W	Overall 210 mg Q2W	All Doses*
Long-term			N=256	N=1304	N=4464

*All Doses includes mixed doses and variable doses

Summary of Adverse Events

Psoriasis Studies, 12-week and 52-week Pools

Week 12	Brodalumab				
	Placebo N=879 n (%)	Ustekinumab N=613 n (%)	140 mg Q2W N=1491 n (%)	210 mg Q2W N=1496 n (%)	All N=3066 n (%)
All treatment-emergent AEs	451 (51.3)	345 (56.3)	845 (56.7)	870 (58.2)	1765 (57.6)
Serious AEs	15 (1.7)	6 (1.0)	29 (1.9)	20 (1.3)	49 (1.6)

Week 52	Brodalumab			
	Ustekinumab N=613 PY=494.7 n (r)	Constant 140 mg Q2W N=280 PY=215.3 n (r)	Constant 210 mg Q2W N=1335 PY=1042.0 n (r)	All N=4012 PY=3445.5 n (r)
All treatment-emergent AEs	1952 (394.6)	853 (396.2)	4142 (397.5)	13826 (401.3)
Serious AEs	42 (8.5)	21 (9.8)	100 (9.6)	285 (8.3)

r = rate per 100 PY

All and Serious Adverse Events

- **Most common AEs at 12 weeks and through 52 weeks**
 - ▶ Nasopharyngitis, upper respiratory tract infection, headache and arthralgia most common
 - ▶ Headache and arthralgia considered adverse drug reactions
- **Serious AEs overall occurred with similar frequency in placebo, ustekinumab and brodalumab in the 12 week pool**
 - ▶ Cellulitis, appendicitis, gastroenteritis, acute pancreatitis most common
- **Serious AEs overall occurred with similar rates in ustekinumab and brodalumab in the 52 week pool**
 - ▶ Cellulitis, MI and cholelithiasis most common

Fatal Events - No Increase in Mortality

- **Long term (through end of study)**
 - ▶ **Brodalumab:** 23 deaths: 12 cardiovascular, 4 completed suicides, 3 accidental deaths, 4 single other events
 - ▶ **Ustekinumab:** 2 deaths: MI, pancreatic cancer
- **Follow-up adjusted rates (per 100 PY)**
 - ▶ **Brodalumab:** 0.4 (52-week)
 - ▶ **Ustekinumab:** 0.4 (52-week)
 - ▶ **Brodalumab:** 0.3 (Long term)
- **Standardized Mortality Ratio (SMR) (95% CI): 0.53 (0.33-0.79)**

Known Risks

- **Exacerbation of existing Crohn's Disease**
- **Infections**
- **Neutropenia**

Psoriasis and Cardiovascular Disease

- **Psoriasis is associated with increased cardiovascular risk factors and cardiovascular events**
 - ▶ Risk factors with increased prevalence in PsO:
 - Obesity
 - Hypertension
 - Smoking
 - Type 2 diabetes
 - Dyslipidemia
 - CV History
- **Increased cardiovascular risk in patients with psoriasis***

Relative Risk (95% CI)

- ▶ Myocardial infarction: 1.70 (1.32 – 2.18)
- ▶ Stroke: 1.56 (1.32 – 1.84)
- ▶ Cardiovascular (CV) mortality: 1.39 (1.11 – 1.74)

Baseline Cardiovascular Risk Factors

Psoriasis Studies

	Placebo N=879 n (%)	Ustekinumab N=613 n (%)	All Brodalumab N=3066 n (%)
Smoking status (former/current)	493 (56)	361 (59)	1680 (55)
Overweight/obese	397 (45)	285 (47)	1425 (47)
BMI >30	387 (44)	282 (46)	1411 (46)
Overweight/obesity preferred term	66 (8)	57 (9)	264 (9)
Hypertension	220 (25)	189 (31)	824 (27)
Dyslipidemia	244 (28)	111 (18)	706 (23)
Glucose intolerance/diabetes	91 (10)	77 (13)	351 (11)
At least one relevant medical history	32 (4)	24 (4)	104 (3)
Ischemic cerebrovascular SMQ	6 (0.7)	9 (1.5)	21 (0.7)
Ischemic heart disease SMQ	27 (3)	16 (3)	88 (3)

SMQ=Standard MedDRA Query

Includes data from patients in Studies 20090062, 20120102, 20120103, 20120104 with ≥1 dose of investigational product

Cardiovascular Risk Factors Were Prevalent in the Brodalumab Psoriasis Studies

Baseline cardiovascular risk factors all patients

	Placebo N=879 n (%)	Ustekinumab N=613 n (%)	All Brodalumab N=3066 n (%)
Risk factor			
0	132 (15)	109 (18)	514 (17)
1	312 (36)	202 (33)	1106 (36)
2	237 (27)	150 (25)	741 (24)
3	124 (14)	84 (14)	419 (14)
4	54 (6)	51 (8)	198 (7)
5	17 (2)	13 (2)	75 (2)
6	3 (0.3)	4 (0.7)	13 (0.4)
Risk factor, category			
0	132 (15)	109 (18)	514 (17)
≥1	747 (85)	504 (82)	2552 (83)
≥2	435 (49)	302 (49)	1446 (47)

Cardiovascular Events of Interest

Psoriasis Studies, 52-Week Pool, Long Term Pool

	52-week Pool		Long Term Pool
	Ustekinumab N=613 n (r)	All Brodalumab N=4019 n (r)	All Brodalumab N=4464 n (r)
Exposure-adjusted	495 PY	3446 PY	8655 PY
Ischemic cerebrovascular disease SMQ	1 (0.2)	7 (0.2)	21 (0.2)
Ischemic heart disease SMQ	5 (1.0)	40 (1.2)	85 (1.0)
Follow-up adjusted	504 PY	3548 PY	9174 PY
Ischemic cerebrovascular disease SMQ	1 (0.2)	11 (0.3)	24 (0.3)
Ischemic heart disease SMQ	6 (1.2)	41 (1.2)	93 (1.0)

MACE

Phase 3 Psoriasis Studies, 12-Week Pool

	Placebo N=842 n (%)	Ustekinumab N=613 n (%)	Brodalumab		
			140 mg Q2W N=1452 n (%)	210 mg Q2W N=1456 n (%)	All Doses* N=2908 n (%)
All MACE events	0	0	3 (0.2)	0	3 (0.1)
CV death	0	0	0	0	0
MI	0	0	2 (0.1)	0	2 (0.1)
Stroke	0	0	1 (0.1)	0	1 (<0.1)

*All Doses includes mixed doses and variable doses

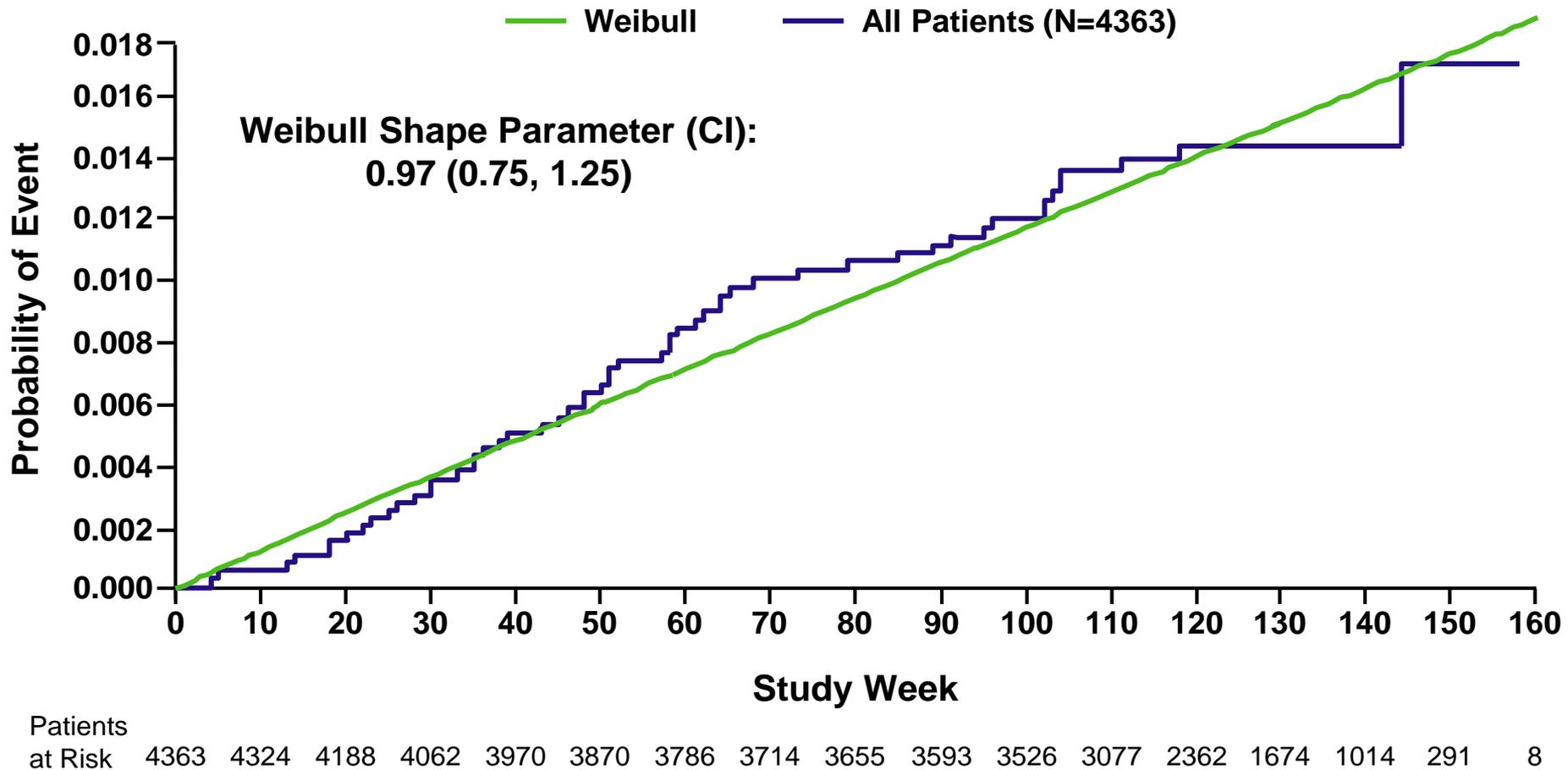
MACE

Phase 3 Psoriasis Studies, 52-Week and Long Term Pools

	52-week Pool		Long Term Pool
	Ustekinumab N=613 n (r)	All Brodalumab N=4019 n (r)	All Brodalumab N=4464 n (r)
Exposure-adjusted	495 PY	3295 PY	7870 PY
All MACE events	2 (0.4)	20 (0.6)	40 (0.5)
CV death	1 (0.2)	2 (0.1)	5 (0.1)
MI	1 (0.2)	14 (0.4)	25 (0.3)
Stroke	0	4 (0.1)	10 (0.1)
Follow-up adjusted	504 PY	3378 PY	8365 PY
All MACE events [95%CI]	2 (0.4) [0.05,1.43]	24 (0.7) [0.46,1.06]	54 (0.6) [0.48,0.84]
CV death	1 (0.2)	3 (0.1)	12 (0.1)
MI	1 (0.2)	16 (0.5)	30 (0.4)
Stroke	0	5 (0.1)	12 (0.1)

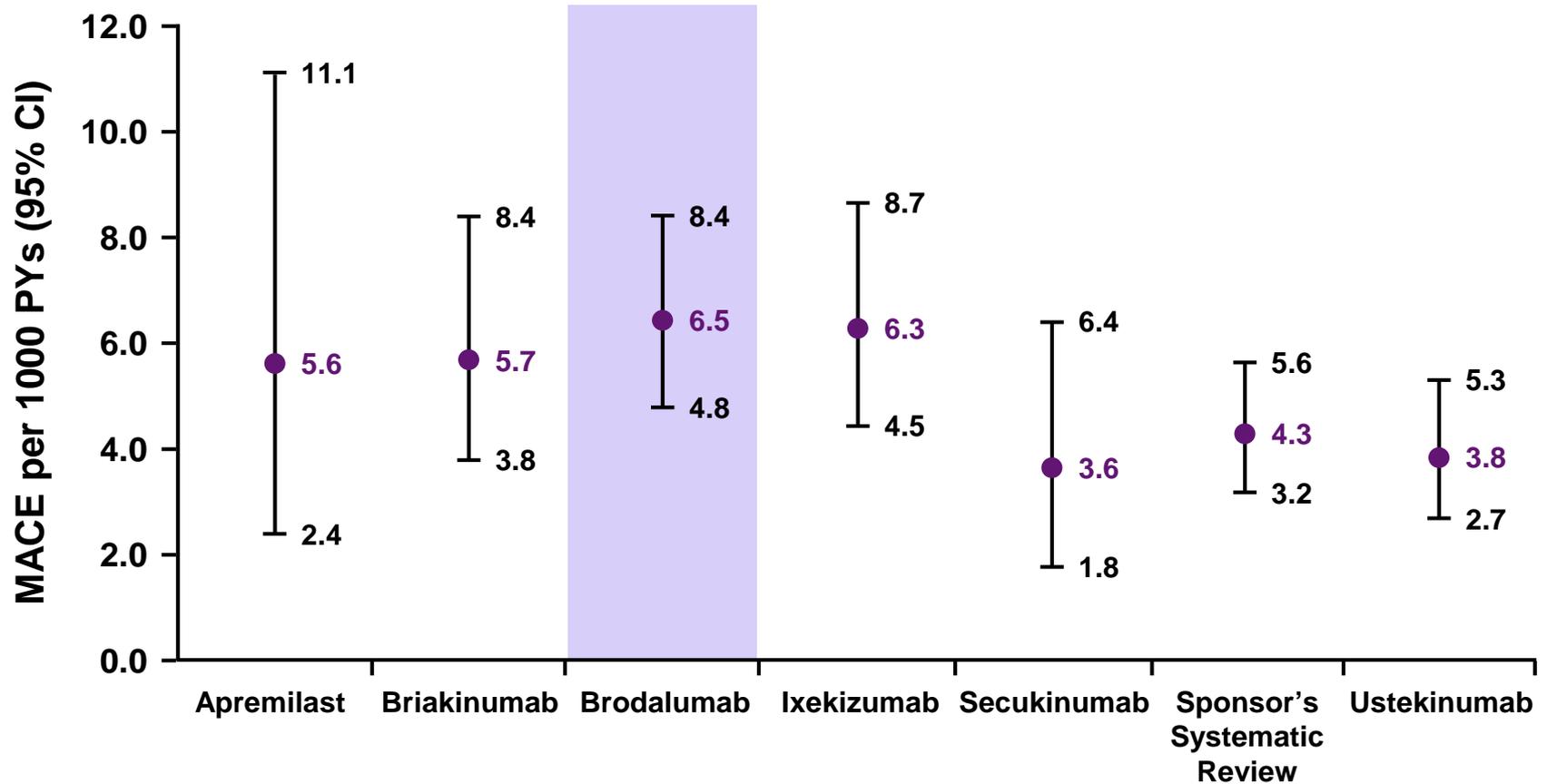
Multiple occurrences of the same event for a patient are counted as multiple events.
 Patients 17001 and 04011 had multiple MACE events.

Time Event Analysis for MACE



DEPI Review of MACE

MACE per 1000 Person-years of Treatment in Psoriasis Clinical Trials



Evidence Does Not Support MACE Causality

- **Direct evidence**

- ▶ Based on few events
- ▶ Confidence intervals overlap

- **Temporality**

- ▶ No temporal pattern
- ▶ Rate constant over time

- **Dose response**

- ▶ No dose trend between 140 mg and 210 mg
- ▶ No CV effects overall or with high doses in nonclinical studies

Evidence Does Not Support MACE Causality

- **Biological plausibility**

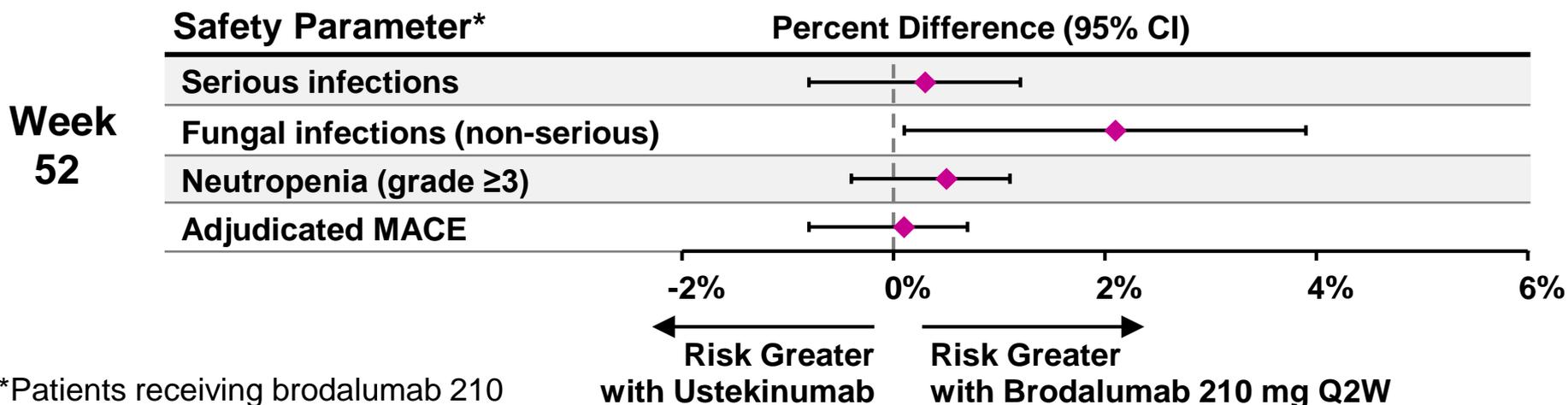
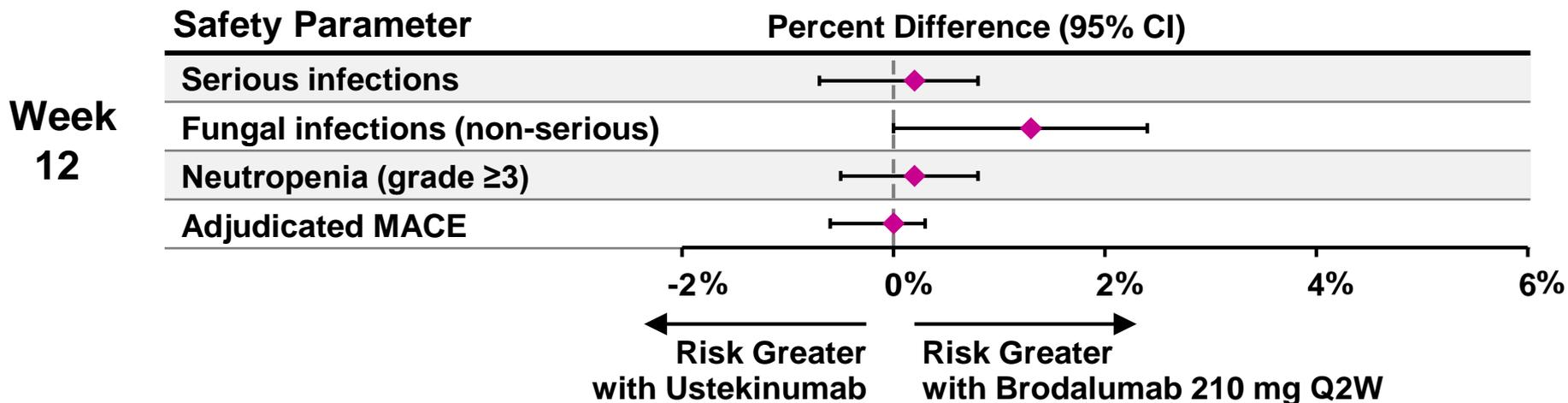
- ▶ Evidence does not support link between MOA and adverse cardiac events
- ▶ No evidence of adverse effects on glucose, lipids, blood pressure, ECG

- **Consistency of findings**

- ▶ No imbalance in overall cardiovascular adverse events
- ▶ MACE not associated with other anti-IL-17 molecules

Risk Summary Plot

AMAGINE 2 and 3, Week 12 and Week 52



*Patients receiving brodalumab 210 mg 2QW ≥ 40 weeks

Conclusions

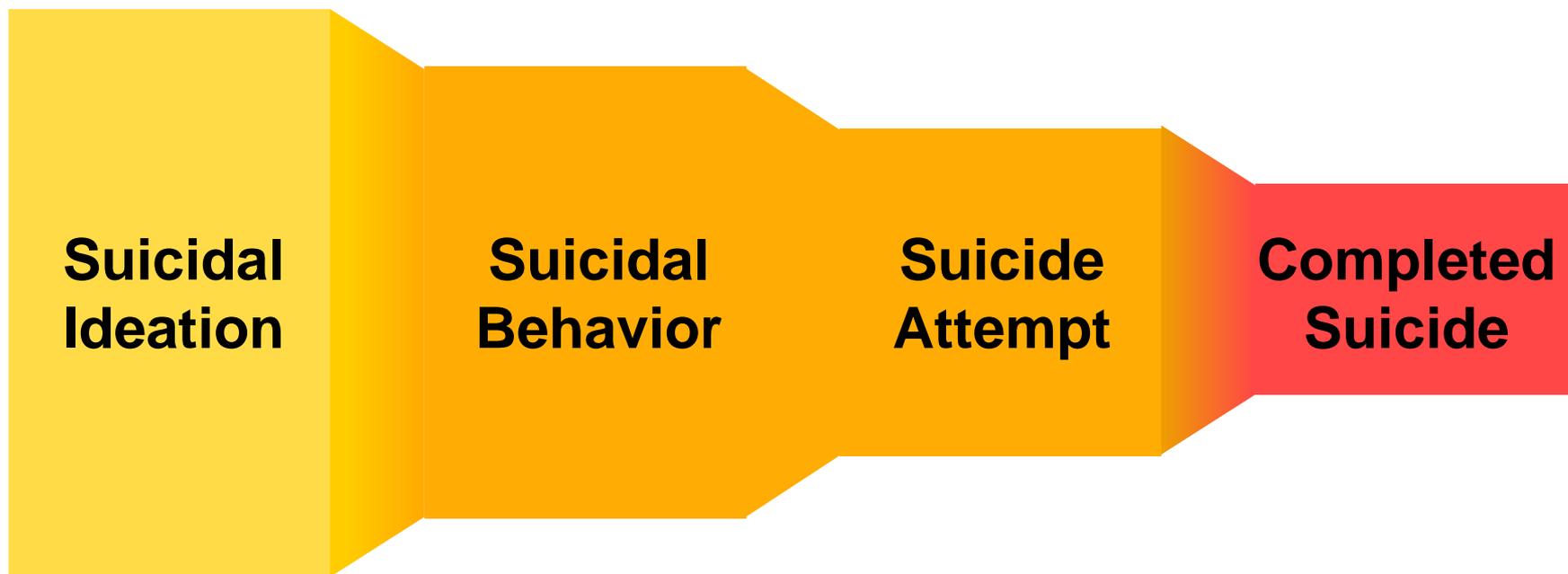
- **Safety profile consistent with agents that target the IL-17 pathway**
- **Risks associated with the exacerbation of Crohn's Disease, infection, and neutropenia are manageable and are described in the proposed label**
- **Analysis of MACE data does not support a causal association with brodalumab**

Suicidal Ideation and Behavior

Lauren B. Marangell, MD

Psychiatrist and President, Brain Health
Consultants

Spectrum of Suicidal Ideation and Behavior

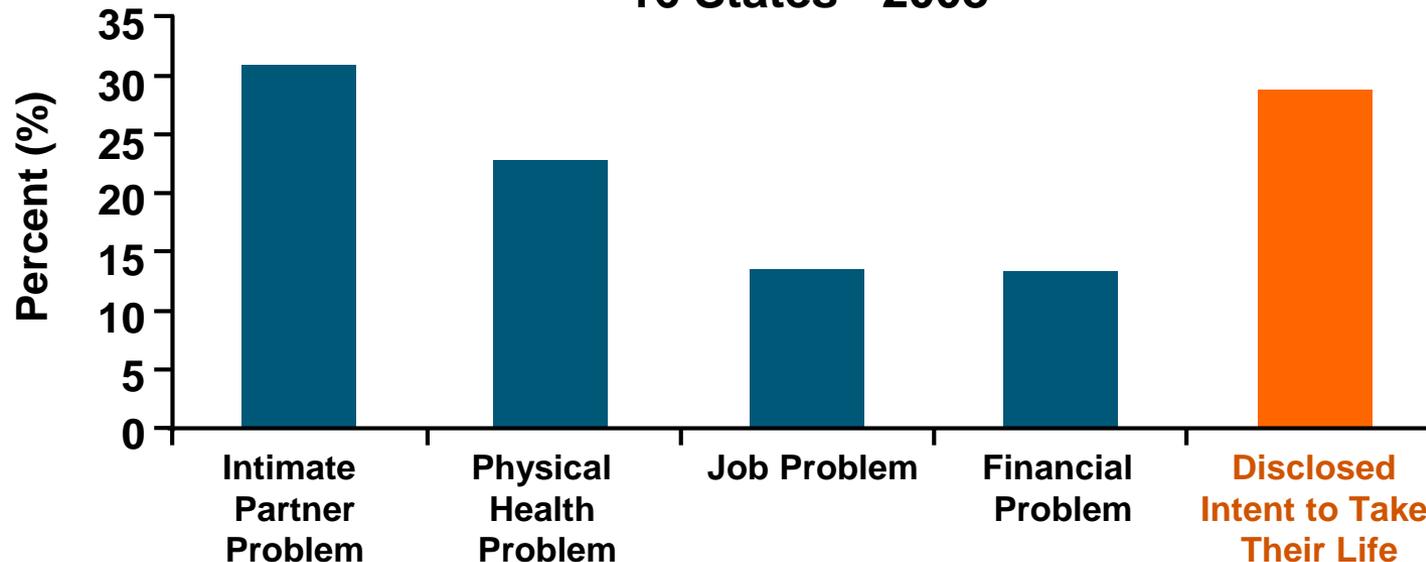


*<http://www.taadas.org/publications/prodimages/Self%20Directed%20Violence%20Surveillance.pdf> Self-directed Violence Surveillance Uniform Definitions And Recommended Data Elements Version 1.0. CDC, 2011

Suicide Risk Factors

- **Psychiatric disorders – most commonly depression, substance abuse, personality disorders and schizophrenia**
- **History of trauma or abuse, major physical illness, previous suicide attempt**
- **Life stressors interact with other risk factors**

**National Violent Death Reporting System
16 States - 2008**



SIB Risk Factors Increased in Psoriasis

- Depression and anxiety increased ~2X
- Increased rates of alcohol abuse
- SIB: ~2X increase

Unlike in other psoriasis development programs, there were no specific exclusion criteria for psychiatric disorders or substance abuse in the brodalumab program

Baseline Psychiatric Co-morbidity

	Placebo N=879 n (%)	Ustekinumab N=613 n (%)	Brodalumab N=3066 n (%)
Psychiatric disorders	150 (17.1)	121 (19.7)	538 (17.5)
Depression	77 (8.8)	68 (11.1)	306 (10.0)
Depressed mood	1 (0.1)	0	1 (0.0)
Major depression	1 (0.1)	0	1 (0.0)
Anxiety	60 (6.8)	32 (5.2)	168 (5.5)
Panic attack	1 (0.1)	2 (0.3)	10 (0.3)

- **~17% of brodalumab patients had baseline psychiatric disorders by medical history in psoriasis studies**
- **23% of brodalumab patients had moderate to severe depression or anxiety at baseline (HADS, AMAGINE-1)**

History of SIB Observations and Actions

- **2012 – Psoriasis Phase 3 program started enrollment**
- **2013/2014 – cluster of SIB events observed and discussed with agencies**
- **No clinical hold**
- **eC-SSRS and PHQ implemented**
 - ▶ 84% of patients in Phase 3 psoriasis program already in uncontrolled open label extension

SIB was Infrequent in Randomized, Placebo-Controlled 12-Week Period – Psoriasis Studies

	Placebo N=879 n (%)	Ustekinumab N=613 n (%)	Brodalumab N=3066 n (%)
Suicidal ideation	0	0	0
Suicide attempt	0	0	1 (0.03)
Completed suicide	0	0	0
Total	0	0	1 (0.03)

- **Ascertainment: routine AE reporting**

Prospective Ascertainment of SIB Does Not Change Controlled Results - Psoriatic Arthritis 16-Week

	Placebo N=320 n (%)	Brodalumab N=639 n (%)
Suicidal ideation	0	1 (0.2)
Suicidal behavior (non-fatal)	0	0
Completed suicide	0	0
Total	0	1 (0.2)

- **Ascertainment with prospective eC-SSRS**
- **These data do not support a causal relationship**

No Imbalance in Neuropsychiatric Disorders in 12 Weeks - Psoriasis Studies

Cluster‡	Placebo N=879 %	Brodalumab N=3066 %
All Psychiatric Clusters	2.16	2.15
All Neurology Clusters	6.37	7.80
Depression	0.80	0.55
Bipolar disorder / Mood fluctuation	0.11	0.13
Anxiety (including panic)	0.23	0.46
Irritability / Hostility / Impulsivity	0	0.03
Insomnia / Sleep disturbance	0.80	0.62
Sedation / Psychomotor retardation	0.34	0.16
Psychosis	0	0.07
Altered mental status	0.23	0.13

‡ One or more MedDRA Preferred Terms highly suggestive for the presence of the cluster name

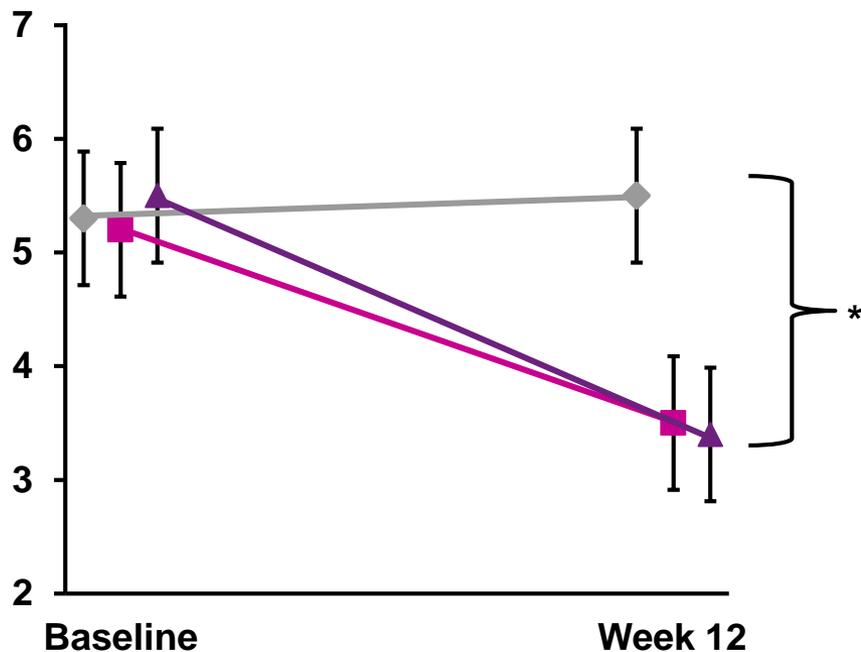
- **No neuropsychiatric safety signal seen in 12 week period**
- **Similarly in psoriatic arthritis, there was no neuropsychiatric signal**

HADS Change from Baseline

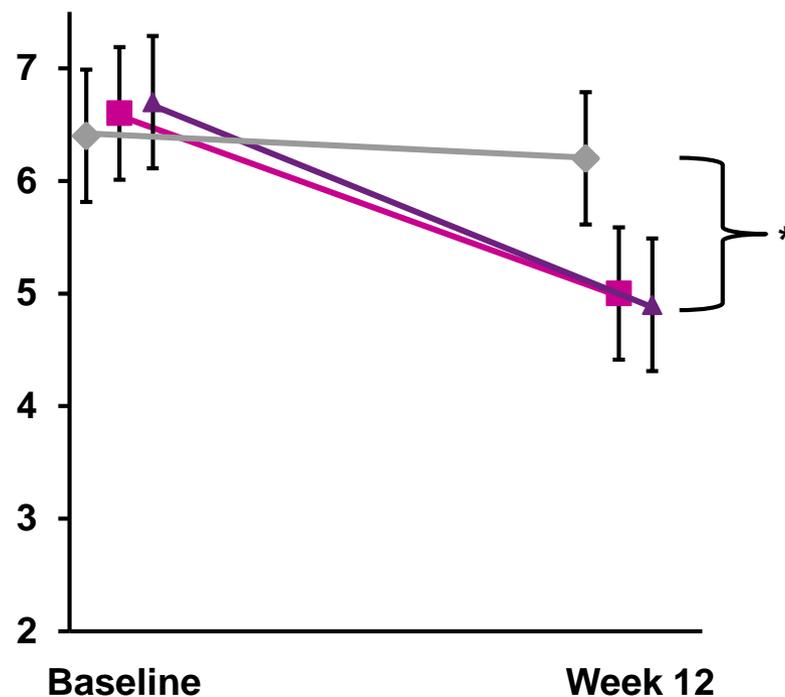
AMAGINE-1, 12-Week Pool

—◆— Placebo —■— 140 mg Q2W —▲— 210 mg Q2W

HADS Depression Subscale (as Observed)



HADS Anxiety Subscale (as Observed)



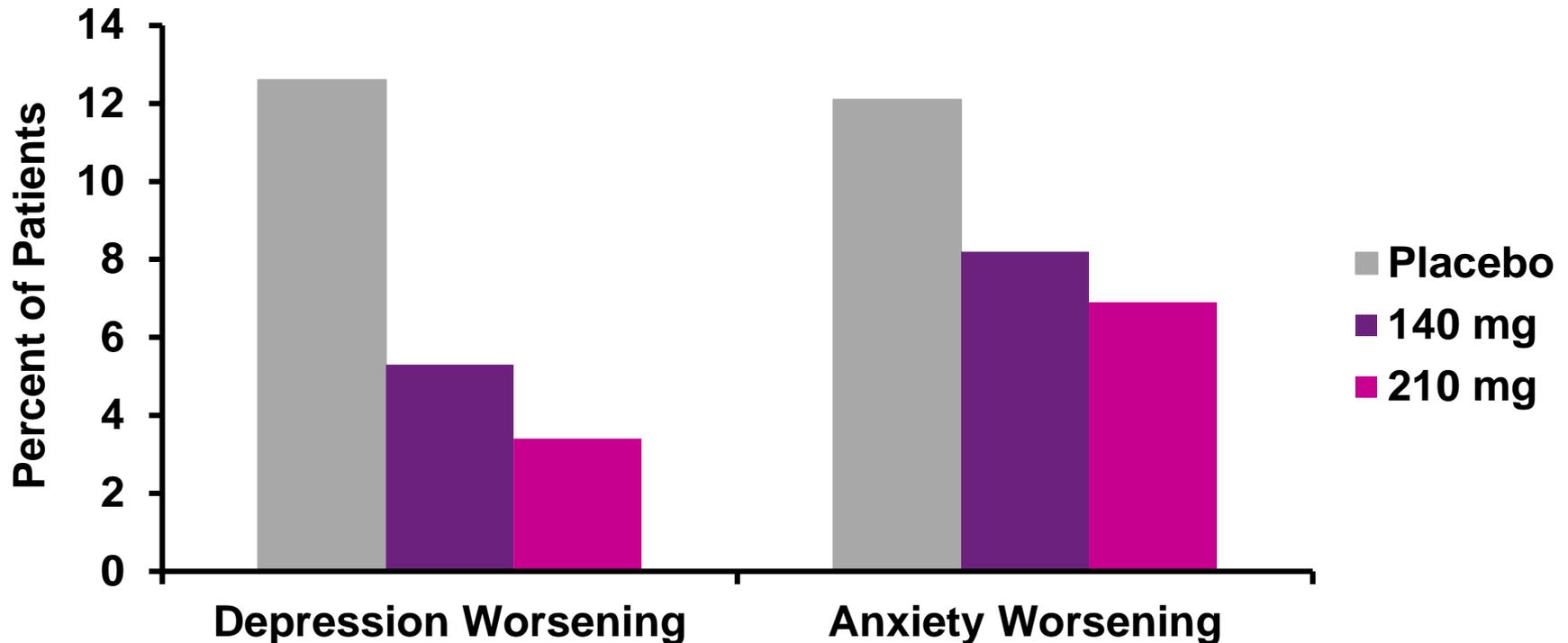
I 95% confidence interval.

* All P values <0.001 for comparisons between brodalumab groups against placebo for both the depression and anxiety subscale scores at week 12.

HADS = Hospital Anxiety and Depression Scale

HADS Depression and Anxiety Worsening

AMAGINE-1, 12 Week Pool



Worsening defined as change from <8 (normal) to ≥ 8 and with ≥ 2 point increase
HADS = Hospital Anxiety and Depression Scale

- **Relatively few worsenings**
- **Not associated with any SIB event**

SIB and Neuropsychiatric Events in Drug-related SIB

	Appearance of Neuropsychiatric AE Within 90 Days	Appearance of SIB Within 90 days	Comments
Antidepressants			Risk tends to decrease after first weeks
Anti-Epileptic AED			May persist
Interferon α			Peaks weeks 4-16
Rimonabant			May persist
Isotretinoin			Median time to onset 12 weeks

No Imbalance in Overall SIB up to 52 Weeks Double-blinded Psoriasis Studies

Follow-up-Adj	Ustekinumab (504 PY) N=613 n (r)	Brodalumab (3546 PY) N=4019 n (r)
Suicidal ideation	1 (0.20)	3 (0.08)
Suicide attempt	2 (0.40)	1 (0.03)
Intentional self-injury (non-suicidal)	0	1 (0.03)
Completed suicide	0	2 ^a (0.06)
Total	3 (0.60)	7^b (0.20)

^a One adjudicated completed suicide as indeterminate-possible unintentional overdose

^b Includes one intentional self injury without suicidal intent

- **These data do not support a differential drug effect**

Neuropsychiatric Disorders up to 52 Weeks Psoriasis Studies

Cluster [‡]	Ustekinumab (504 PY) N=613 r	Brodalumab (3549 PY) N=4019 r
All Psychiatric Clusters	9.9	8.0
All Neurology Clusters	22.6	22.4
Depression	3.8	2.1
Bipolar disorder/mood fluctuation	0	0.2
Anxiety (including panic)	1.8	2.2
Irritability/hostility/impulsivity	0	0.2
Insomnia/sleep disturbance	2.6	1.7
Sedation/psychomotor retardation	0.4	0.5
Psychosis	0.2	0.1
Altered mental status	0	0.3

[‡] One or more MedDRA Preferred Terms highly suggestive for the presence of the cluster name

Neuropsychiatric Disorders in Long-term Psoriasis Studies

Cluster‡	52 Week Brodalumab (3549 PY) N=4019	Long Term Brodalumab (9174 PY) N=4464
	r	r
All Psychiatric Clusters	8.0	6.3
All Neurology Clusters	22.4	14.1
Depression	2.1	2.0
Bipolar disorder / Mood fluctuation	0.2	0.1
Anxiety (including panic)	2.2	1.4
Irritability / Hostility / Impulsivity	0.2	0.1
Insomnia / Sleep disturbance	1.7	1.3
Sedation / Psychomotor retardation	0.5	0.2
Psychosis	0.1	0.1
Altered mental status	0.3	0.2

‡One or more MedDRA Preferred Terms highly suggestive for the presence of the cluster name

Rates of Ideation and Attempt Increase after C-SSRS Implementation – Psoriasis Studies

	52 Week Brodalumab (3546 PY) N=4019 n (r)	Long Term Brodalumab (9162 PY) N=4464 n (r)
Suicidal ideation	3 (0.08)	22 (0.24)
Suicidal attempt	1 (0.03)	10 (0.11)
Intentional self-injury (non-suicidal)	1 (0.03)	1 (0.01)
Completed suicide	2 ^a (0.06)	4 ^a (0.04)
Total	7^b (0.20)	34^b (0.37)

^a One adjudicated completed suicide as indeterminate-possible unintentional overdose

^b Includes one intentional self injury without suicidal intent

- **Of 10 attempts, only 1 required medical attention**
- **Long-term neuropsychiatric AEs were consistent with 52 week**

Completed Suicides

- **4 in psoriasis studies, one of which was indeterminate**
- **4 males**
- **Age 39 to 59 years old**
- **Time from first dose brodalumab 97 to 845 days**
- **All had psychiatric disorder or stressors**

- **1 in rheumatoid arthritis program and 1 psoriatic arthritis – addressed in the briefing book**

Study Design Impacted the SIB Observations

- **Absence of psychiatric exclusion criteria led to a population with higher baseline risk factors for SIB**
- **Exposure to brodalumab**
 - ▶ Disproportionate randomization and rescue to brodalumab
 - ▶ Substantial exposure to brodalumab in long-term extension
- **Variability**

Recent Approvals Have Observations of SIB

Product	Events	Rate Per 100 PY	95% CI
Apremilast[†]	1 completed on placebo	0.052-0.062	(0.002, 0.345) to (0.001, 0.288)
Secukinumab[‡]	1 completed in Screening	0.034	(0.001, 0.190)
Ixekizumab[¶]	10 attempts on active	0.15 [∞]	(0.072, 0.276)
	1 attempt on placebo	0.55 [∞]	(0.014, 3.064)
Brodalumab	4 completed on active	0.044	(0.012, 0.112)
	10 attempts on active	0.11	(0.052, 0.201)

[†] Apremilast Medical Review, Psoriasis, 2014, Table 29 (Placebo 0-16w and apremilast 30mg BID 0-52w) was used to estimate the incidence rate range, while the apremilast Prescribing Information, 2015, Section 5, indicated 1 suicide occurred in the psoriasis program.

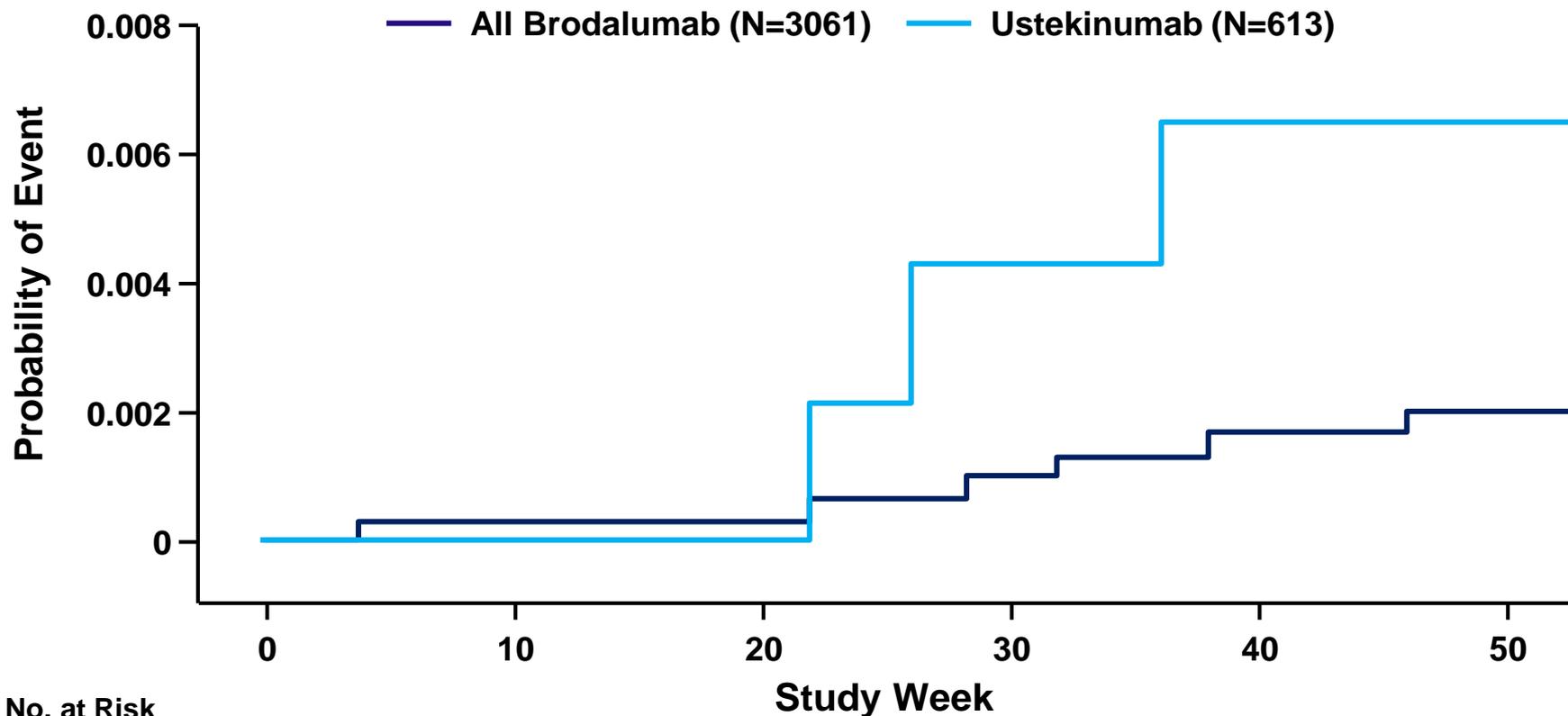
[‡] Secukinumab Advisory Committee Briefing Book, 2014, Table 5-14 (Pool B, through ≥52w) was used to estimate the exposure, and Section 5.5.6 indicated 1 suicide in the psoriasis program.

[¶] Ixekizumab Summary Review, Draft, 2016 p15 describes rates for attempted suicide during the psoriasis program. No completed suicides were noted.

[∞] Patient-year not provided instead back-calculated from the rate and the number of attempts.

Time to First SIB Event From First Active Dose Through Week 52

AMAGINE-2 and AMAGINE-3



No. at Risk

	0	10	20	30	40	50
Brodalumab	3061	3043	2969	2880	2818	2749
Ustekinumab	613	608	589	460	454	446

N = number of subjects in Studies 20120103 and 20120104 with ≥ 1 dose of active investigational product.

"All brodalumab" group includes subjects who received ≥ 1 dose of brodalumab through week 52, and excludes subjects who initially randomized to ustekinumab then switched to brodalumab.

"Ustekinumab" group includes subjects who initially randomized to "Ustekinumab" and received ≥ 1 dose of ustekinumab. For the subjects who switched to brodalumab, they were censored at the time they switched.

Biological Mechanism for Brodalumab Causality of SIB Events Unlikely

- **No CNS toxicity in pre-clinical studies**
- **While some pro-inflammatory cytokines have been linked to depression, IL-17 has not**
 - ▶ Blockade of the IL-17 receptor prevents IL-17 downstream effects
- **Controlled clinical trial data do not indicate neuropsychiatric effects of brodalumab**

Evidence Does Not Support SIB Causality

- **Direct evidence**

- ▶ No imbalance in randomized placebo-controlled or active comparator controlled in a very large dataset
- ▶ No imbalance in rates of neuropsychiatric events in either controlled phase as would be expected with an agent with a causal association to SIB

- **Temporality**

- ▶ Did not occur in first 12 weeks
- ▶ Rates stable until implementation of the eC-SSRS

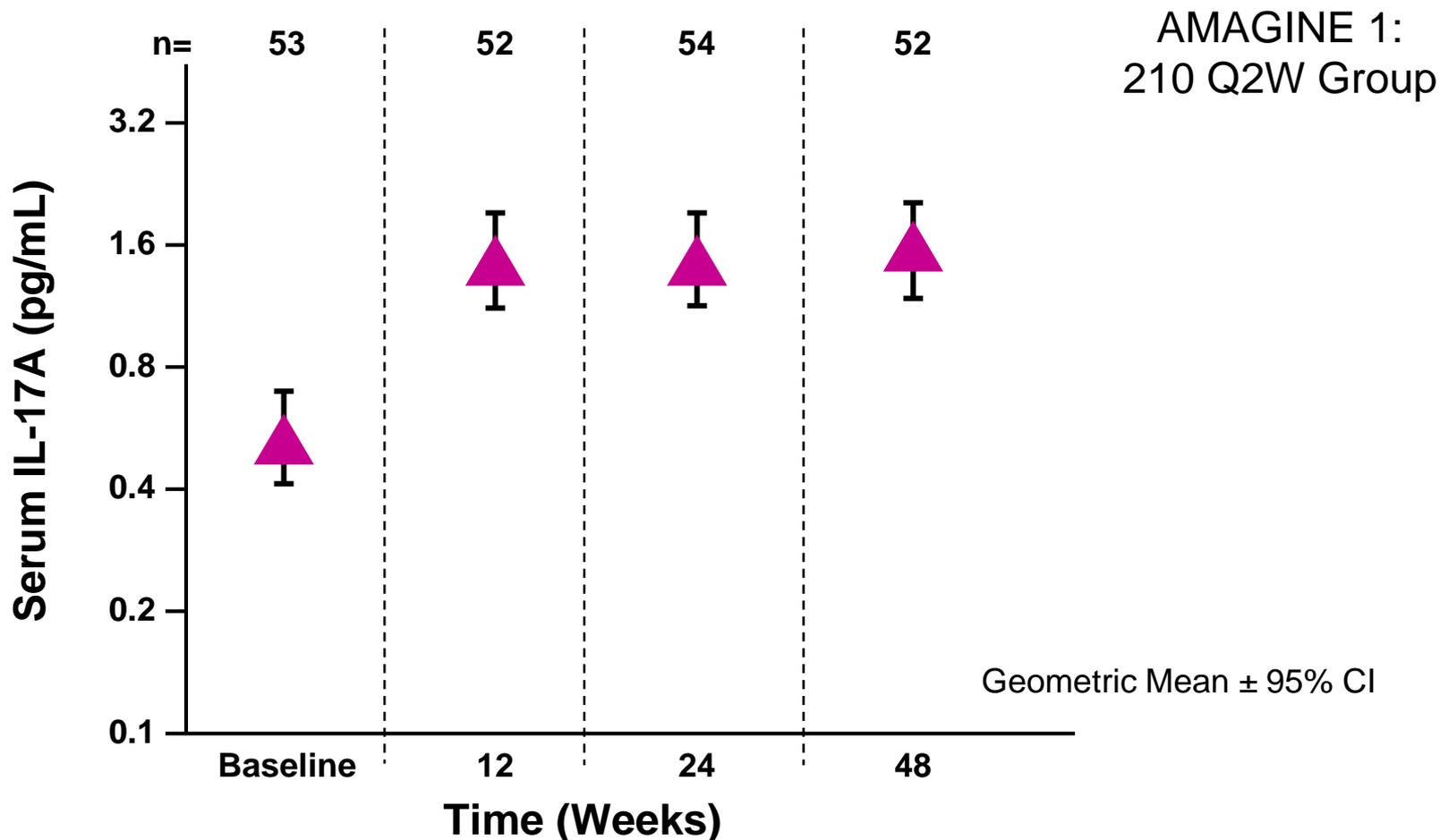
- **Biological plausibility**

- ▶ Clinical context does not support a biologic effect

IL-17 Signaling and Safety

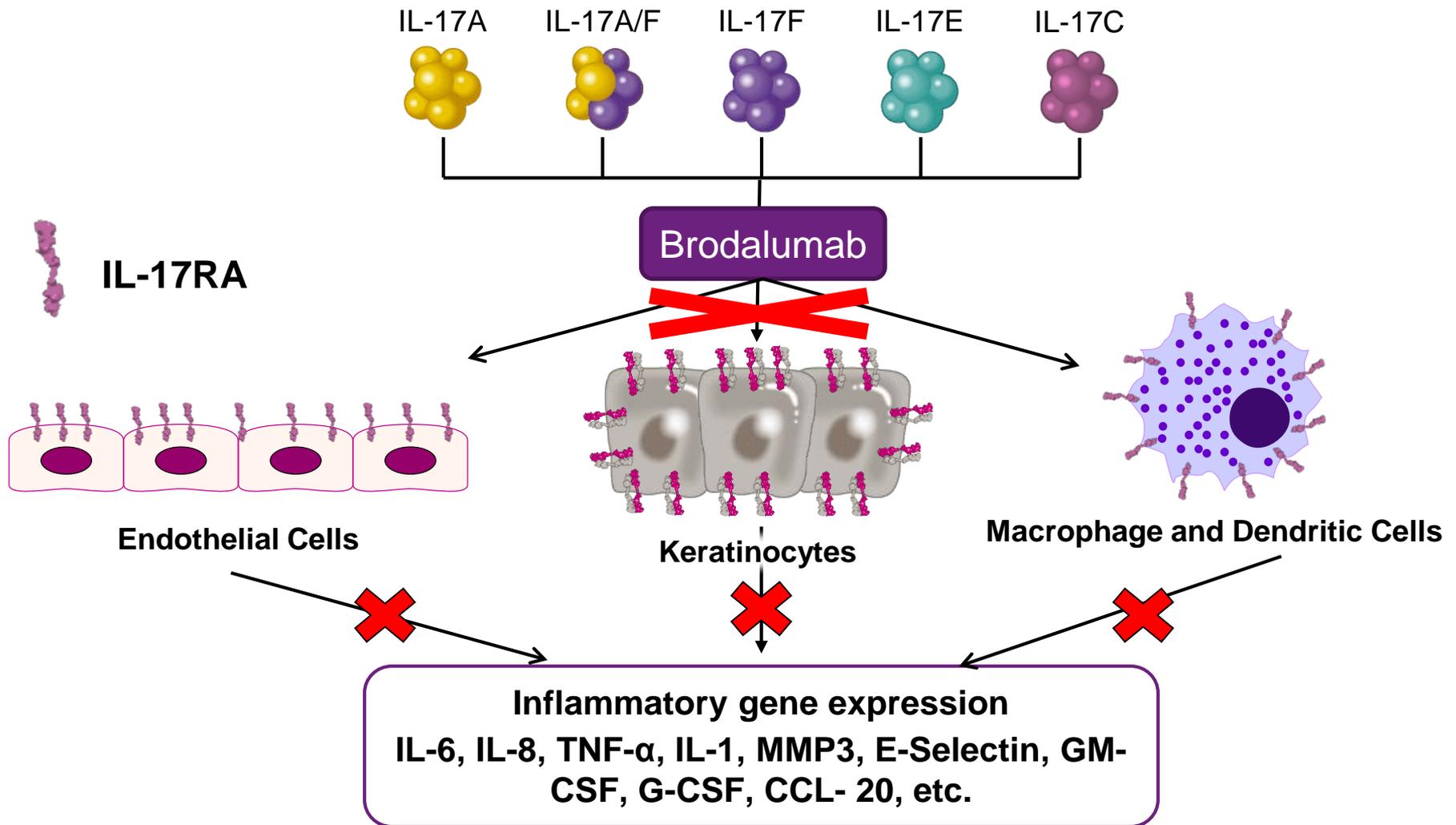
James B. Trager, PhD
Vice President, Research
Valeant

Brodalumab Blockade of IL-17RA Elevates Serum IL-17A Levels



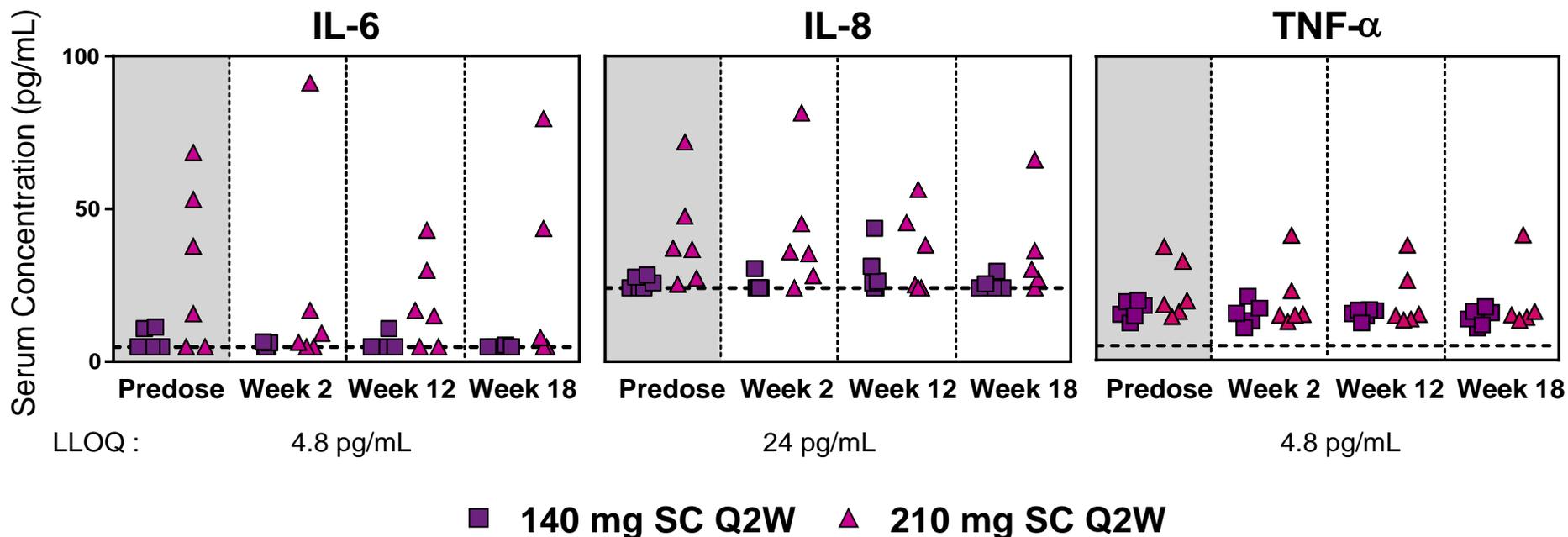
IL-17A elevation is consistent with blockade of receptor-mediated clearance through IL-17RA

IL-17 Signaling Blockade Inhibits Induction of Downstream Inflammatory Factors



Brodalumab Does Not Alter Levels of Serum Cytokines Induced by IL-17 Signaling

Serum cytokine levels assessed in a Phase I study in rheumatoid arthritis



- Minimal changes after repeated SC brodalumab administration
- Same observations after IV administration (420 and 700 mg), and for other IL-17 inducible factors (E-selectin, VEGF, MMP3, YKL-40)

No Established Link Between IL-17 Signaling Blockade and Depression or SIB

- **Brodalumab did not affect downstream cytokines associated with depression and SIB**
 - ▶ Serum levels of IL-6 and other cytokines have been linked with depression and SIB, though correlations are inconsistent across studies^{1,2}
- **Human studies show no consistent association between serum IL-17 and depression**
- **IL-17 is unlikely to act directly upon the CNS**
 - ▶ IL-17A passive diffusion into the CNS limited due to its size; active transport is receptor-dependent and would be blocked by brodalumab
 - ▶ No brodalumab-related CNS toxicity or inflammation observed in pre-clinical studies
 - ▶ Clinical data do not indicate neuropsychiatric effects of brodalumab

¹ Serafini et al., *Eur Neuropsychopharmacol* 2013; ² Ganança et al., *Psychoneuroendocrinology* 2016.

Brodalumab is Unlikely to Promote MACE

- **Clinical and nonclinical brodalumab studies showed no perturbation of cardiac function**
 - ▶ No effect on ECG or histopathology in repeat dose toxicity studies
 - ▶ No safety signals in routine ECG monitoring in psoriasis clinical studies
- **Literature suggests that IL-17 signaling blockade by brodalumab would not promote MACE**
 - ▶ Studies in both humans and animal models indicate that localized IL-17 signaling is atherogenic, and a risk factor for MACE

Risk Management

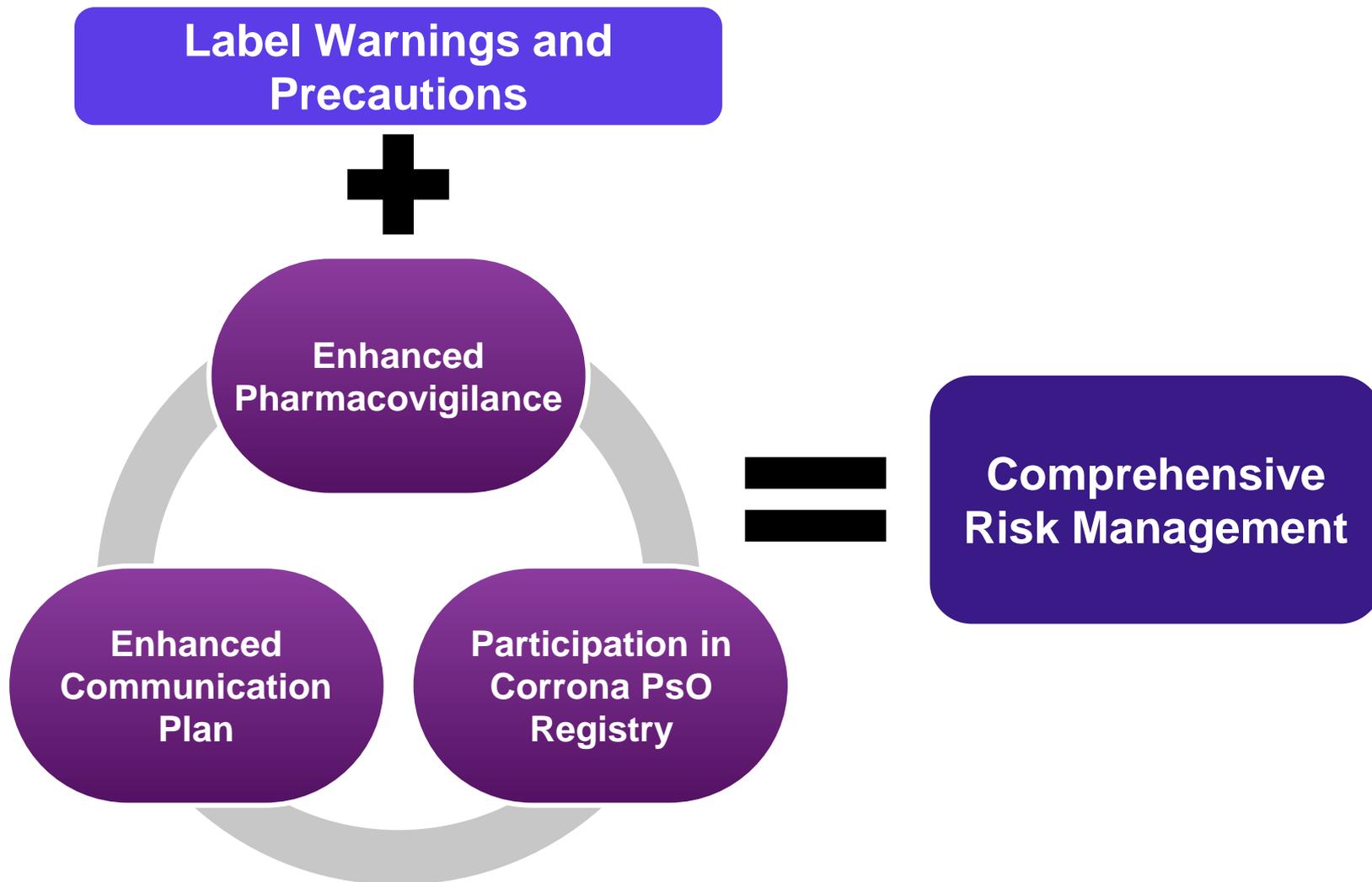
Tage Ramakrishna, MD

Chief Medical Officer

President of Research and Development, Quality

Valeant

Proposed Comprehensive Risk Management Plan



Elements of Proposed SIB Label Language

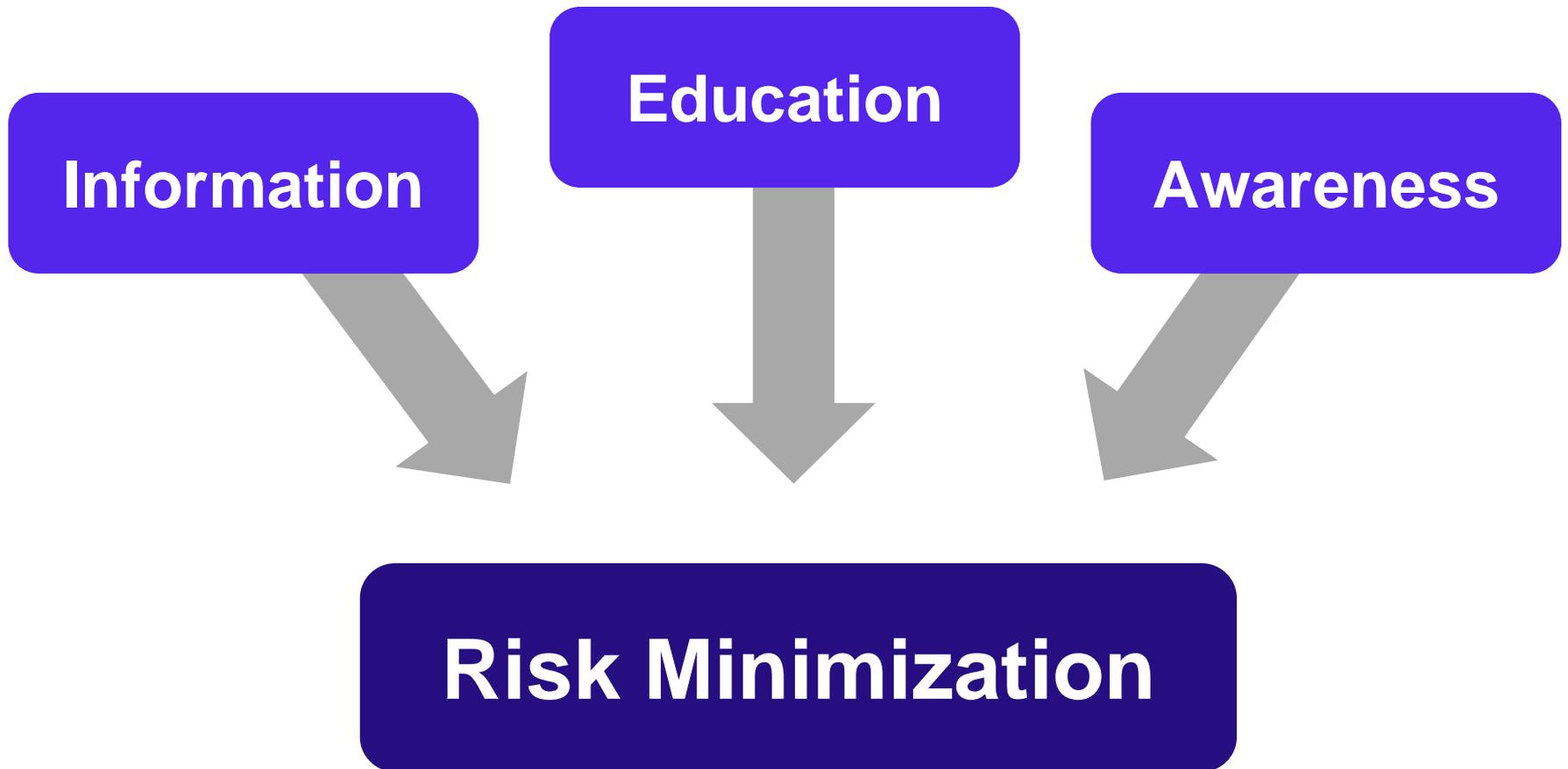
- **SIB events reflected in the warnings and precautions section of the label**
- **Instruct prescribers to evaluate all patients for signs of SIB and consider referral to medical health professionals**
- **Inform patients and caregivers to seek medical advice if mood changes emerge**

Enhanced Pharmacovigilance

- **Key Elements:**

- ▶ Targeted follow-up questionnaires for SIB and MACE
- ▶ Quarterly review of cumulative post-marketing safety data by an independent expert panel, including psychiatrists, cardiologists, and dermatologists

Enhanced Communication Plan



Enhanced Communication Components

- **Medication guide**
- **Communication plan**
 - ▶ Dear Healthcare Provider Letter
 - ▶ Dear Professional Society Letter
 - ▶ Healthcare Provider Fact Sheet
 - ▶ Patient Wallet Card
 - ▶ Healthcare Provider Education Brochure
 - ▶ Website

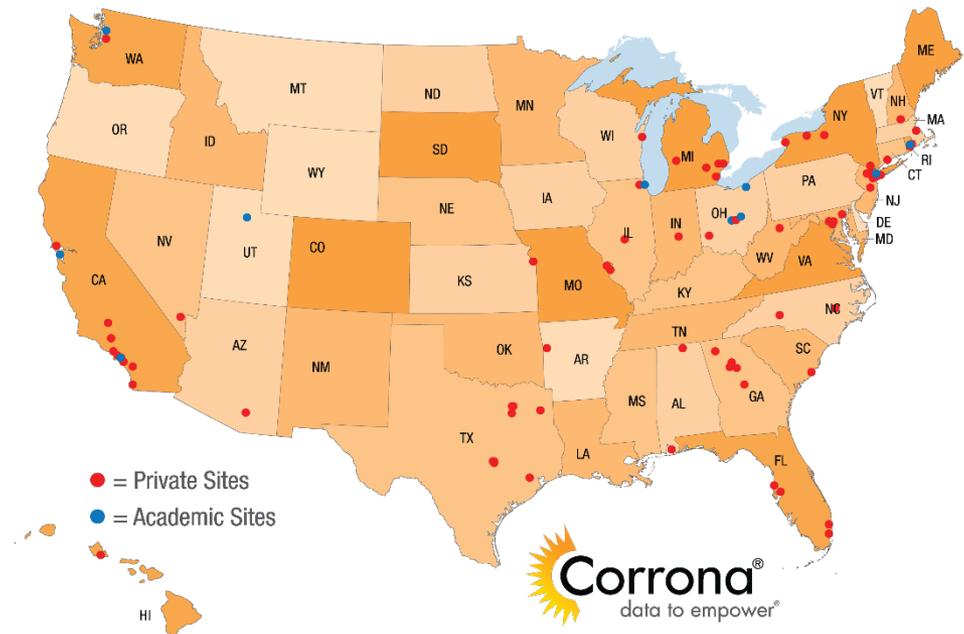
Independent Psoriasis Registry

- **Valeant is in active discussions to join the Corrona registry**
- **Corrona psoriasis registry was developed in collaboration with the National Psoriasis Foundation, independent from pharmaceutical company ownership**
- **Comparative cohorts (e.g. TNF-inhibitors, IL-17A inhibitors) would allow contextualization of safety concerns**

Corrona Psoriasis Registry Update

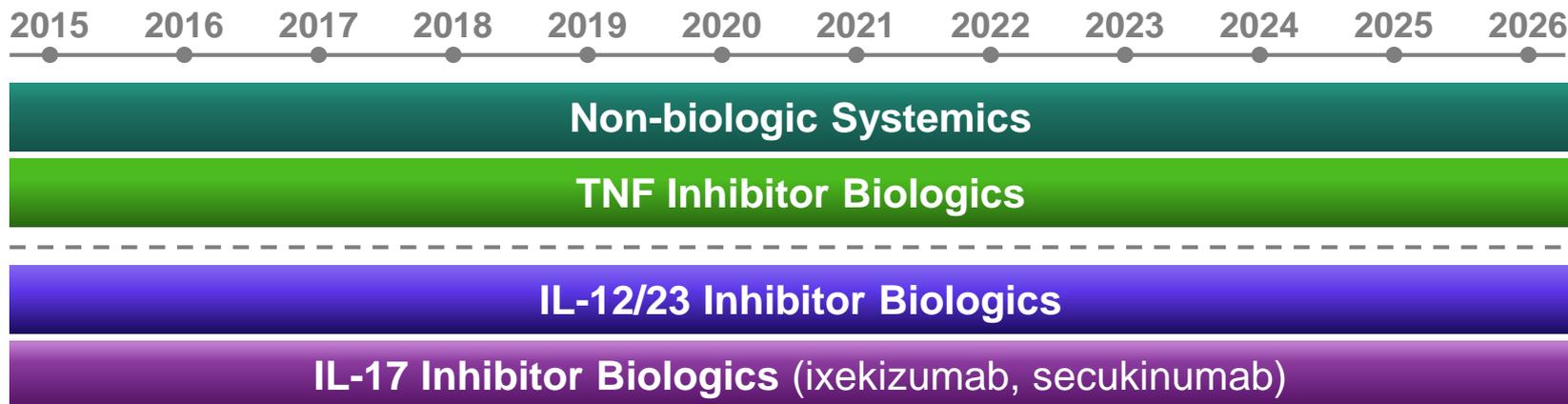
- **Launched with First Patient In April 2015**
- **Network of 120 U.S. dermatology sites and continuing to grow**
- **Over 1650 patients enrolled as of July 1st, 2016**
- **By 2016 year end, Corrona anticipates >150 sites**
- **Anticipated total recruitment >10,000 patients**

Corrona Sites from Inception of the Psoriasis Registry



Corrona Psoriasis Registry Design

Note: Subject to change based on new drug approvals



- **Serious Adverse Events reported with supporting medical records, including:**
 - Nonfatal SAEs: MACE, malignancies, serious infections, anaphylaxis/severe reactions, other life-threatening/important events (e.g. seizure, blood disorder, suicide attempt)
 - Fatal SAEs with cause of death (e.g. CV-related, infection, renal failure, end stage COPD, suicide)
- **Data collected from dermatologists and patients at routine clinical visits**

Proposed Comprehensive Risk Management

Label	Enhanced PV	Communication	Corrona
Warnings and Precaution Labeling <ul style="list-style-type: none">• SIB events reflected in the warnings and precautions section of the label• Instruct prescribers to evaluate all patients for signs of SIB and consider referral to medical health professionals• Inform patients and caregivers to seek medical advice if mood changes emerge	Enhanced Pharmacovigilance Program <ul style="list-style-type: none">• Targeted follow-up questionnaires for SIB and MACE• Quarterly data analysis and review using independent external experts	Enhanced Communication Program <ul style="list-style-type: none">• Medication Guide• Dear Professional Society Letter• Dear Healthcare Provider Letter• HCP Brochure• HCP Factsheet• Patient Wallet Card• Website	Observational study <ul style="list-style-type: none">• Comparing safety data across multiple biologics treating Psoriasis including newly approved anti-IL-17A products (ixekizumab, secukinumab)

Benefit-Risk

Kim Papp, MD, PhD, FRCPC
President, Probitry Medical Research

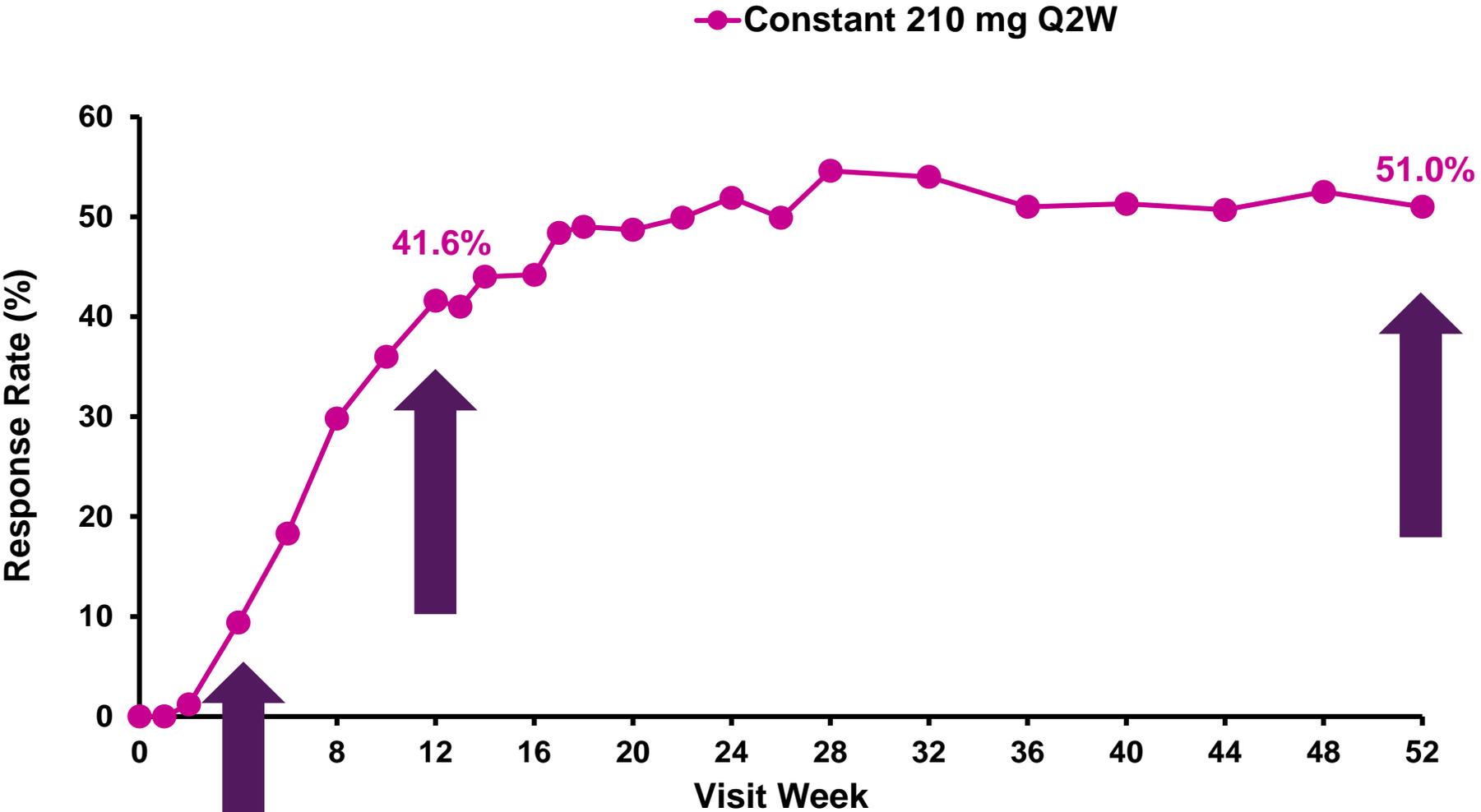
Baseline BSA Involvement 92%



Week 4 (PASI90)

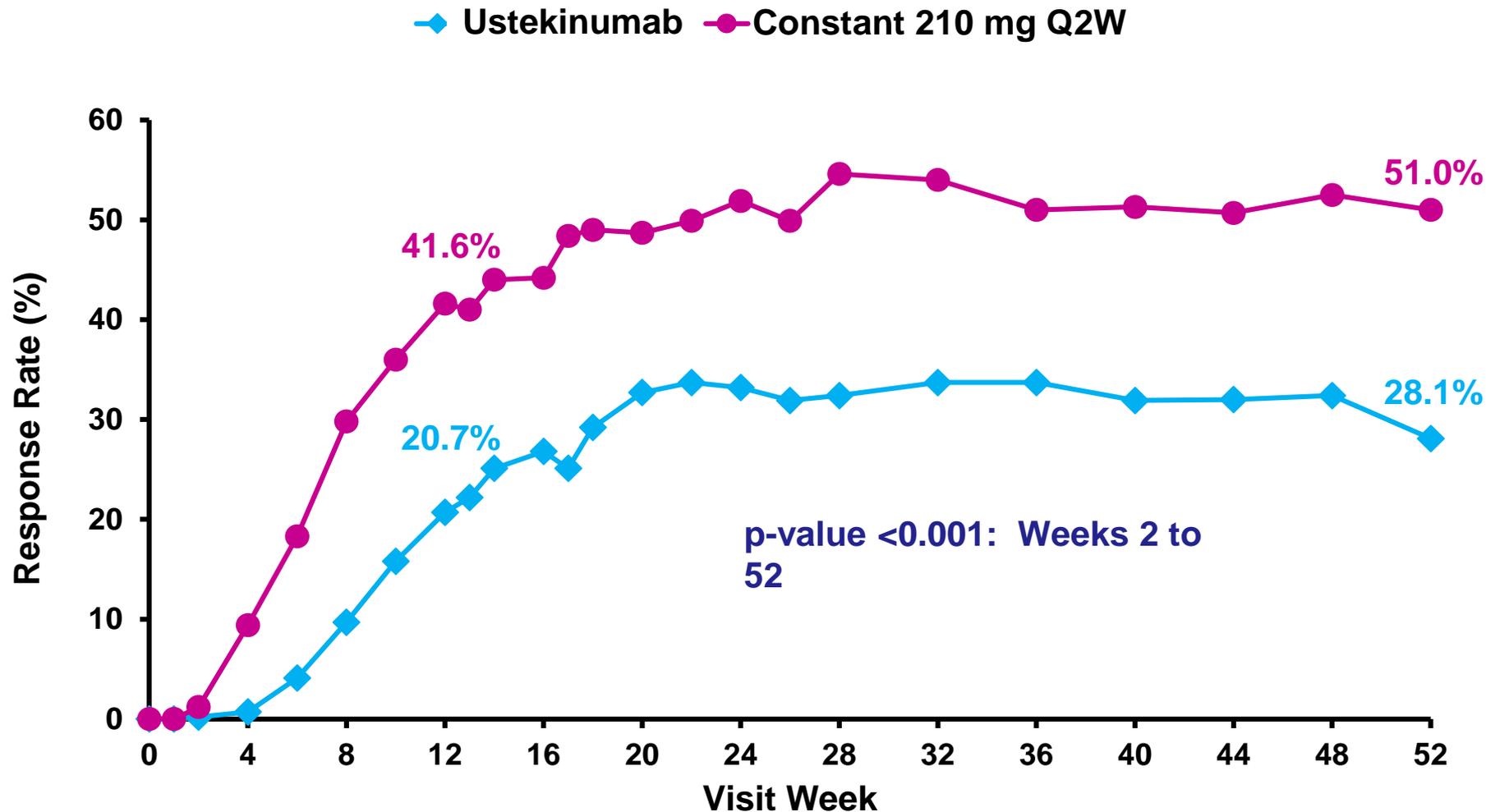


Complete Skin Clearance: Brodalumab 210mg



AMAGINE-2 and AMAGINE-3

Complete Skin Clearance: Brodalumab 210 mg Superior to Ustekinumab



Baseline BSA Involvement 92%



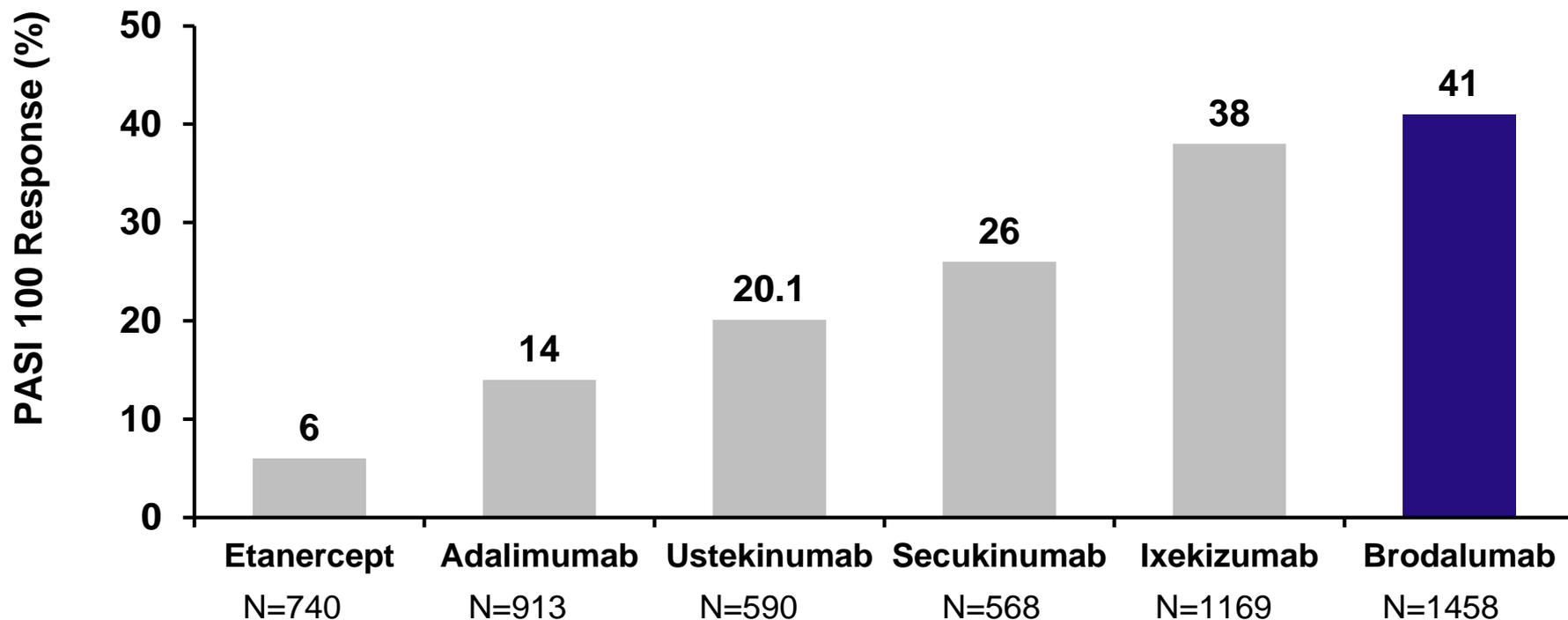
Week 12 (PASI100)



Week 52 (PASI100)



PASI 100 Comparison (12 Week)



Etanercept : FDA Statistical Review, Summary Basis of Approval for Ixekizumab Table 21 and 22 (http://www.accessdata.fda.gov/drugsatfda_docs/nda/2016/125521Orig1s000StatR.pdf)

Secukinumab 300 mg: Novartis Advisory Committee, Advisory Committee Figure 5-9 Weighted mean (<http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/DermatologicandOphthalmicDrugsAdvisoryCommittee/UCM419023.pdf>)

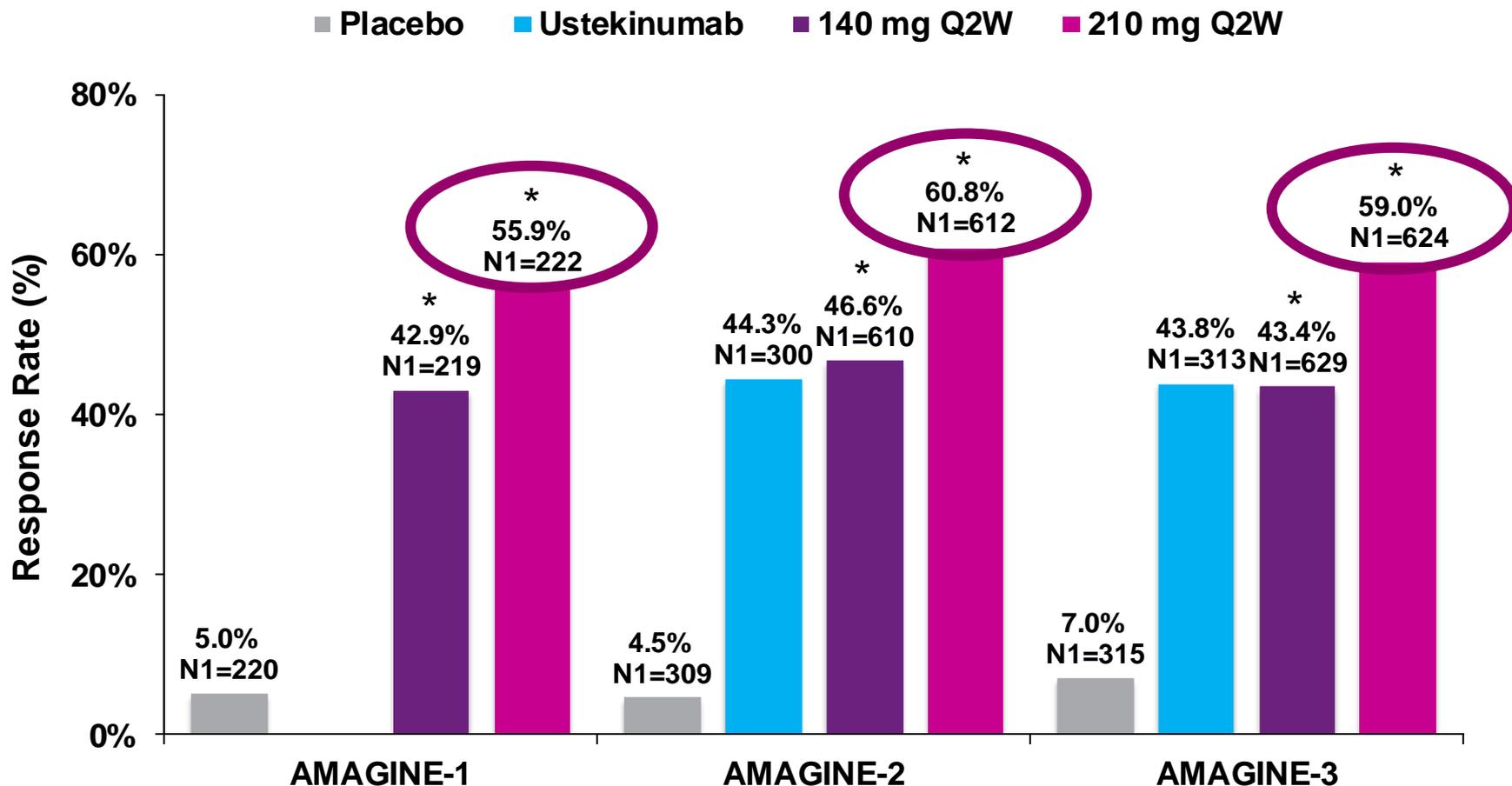
Adalimumab: Menter, Alan, et al., Journal of the American Academy of Dermatology 58.1 (2008): 106-115

Ustekinumab: AMAGINE – 2 and -3 results.

Ixekizumab: Package Insert, FDA Statistical Review, Summary Basis of Approval for Ixekizumab (http://www.accessdata.fda.gov/drugsatfda_docs/nda/2016/125521Orig1s000StatR.pdf) Table 1

Brodalumab: AMAGINE 1, -2, -3

DLQI (Dermatology Life Quality Index) Higher Patient Satisfaction with Brodalumab 210 mg Q2W



DLQI response = score 0/1

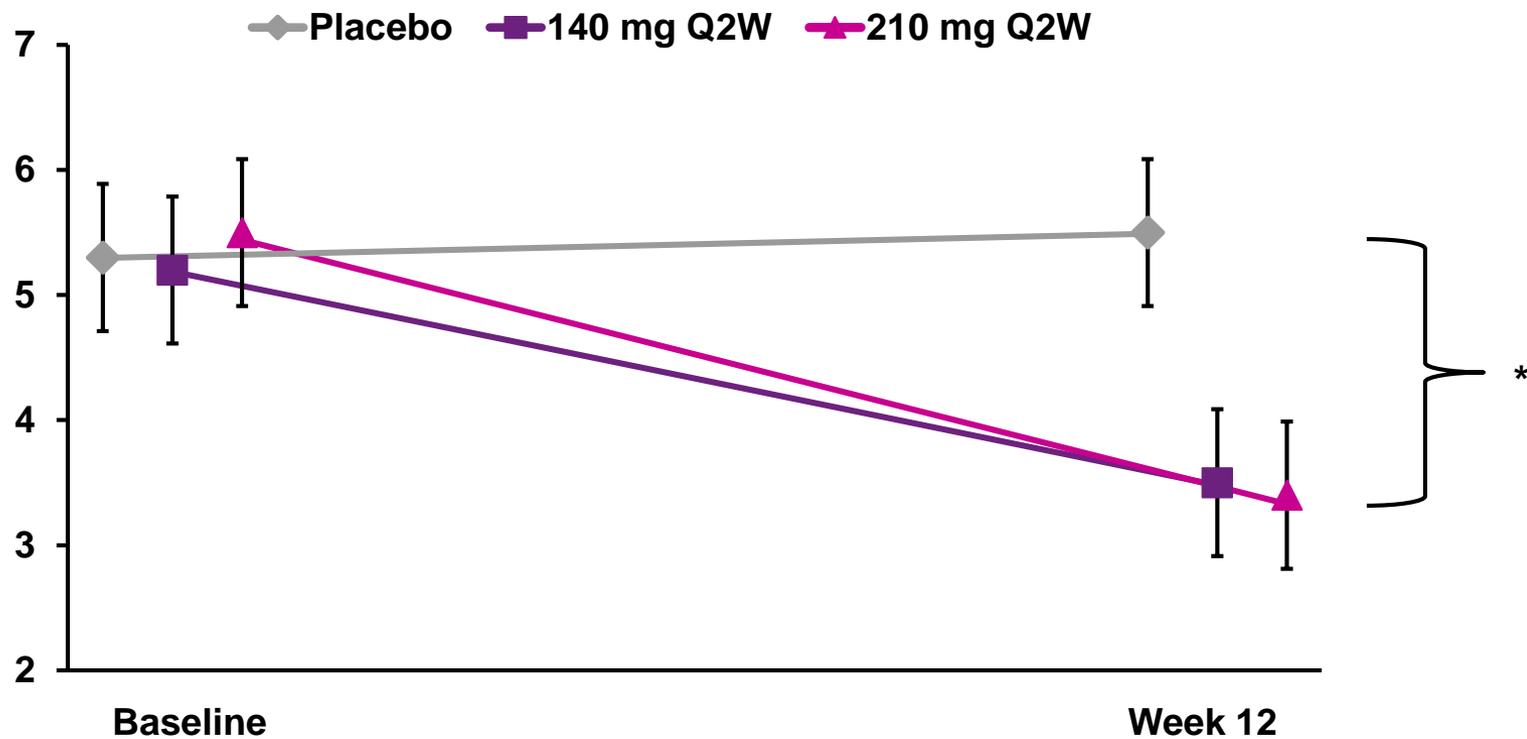
* p<0.001 vs Placebo

Week 12

HADS Change from Baseline

AMAGINE-1, 12-Week Pool

HADS Depression Subscale (as Observed)



I 95% confidence interval.

* All *P* values <0.001 for comparisons between brodalumab groups against placebo for both the depression and anxiety subscale scores at week 12.

Benefits of Brodalumab 210 mg Q2W

- **Rapid onset of action**
- **Significant improvement in skin clearance as measured by PASI-100 (>50% within 1 year)**
- **Patients with complete clearance were nearly double that of Stelara (ustekinumab)**
- **Robust durability of effect**
- **Significant improvement in QOL and depression**

Expected and Manageable Risks

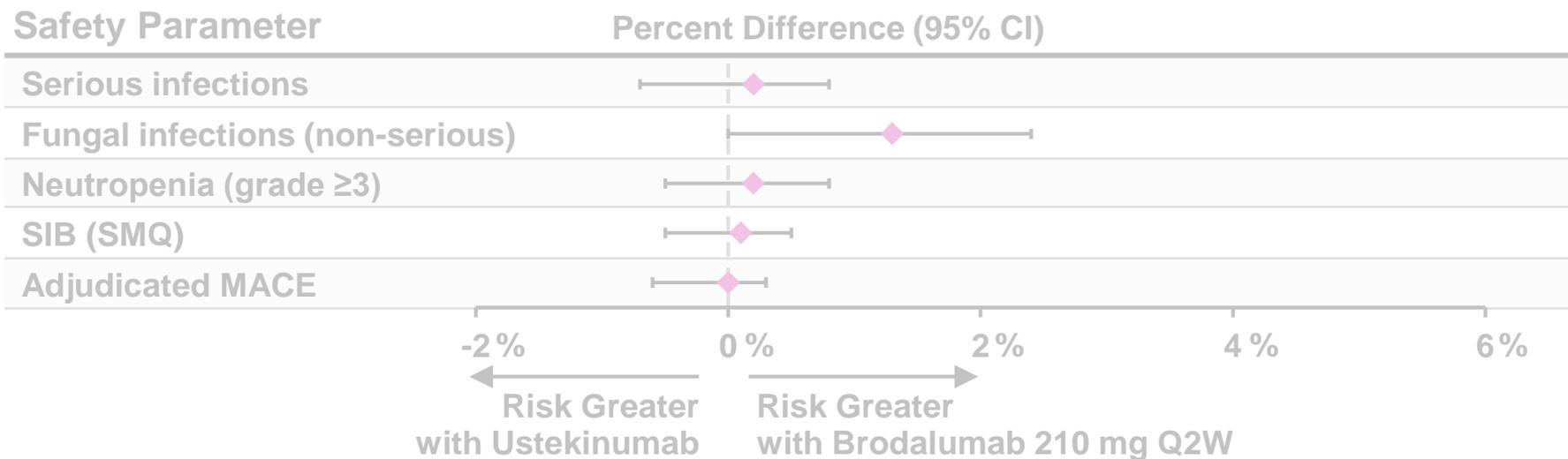
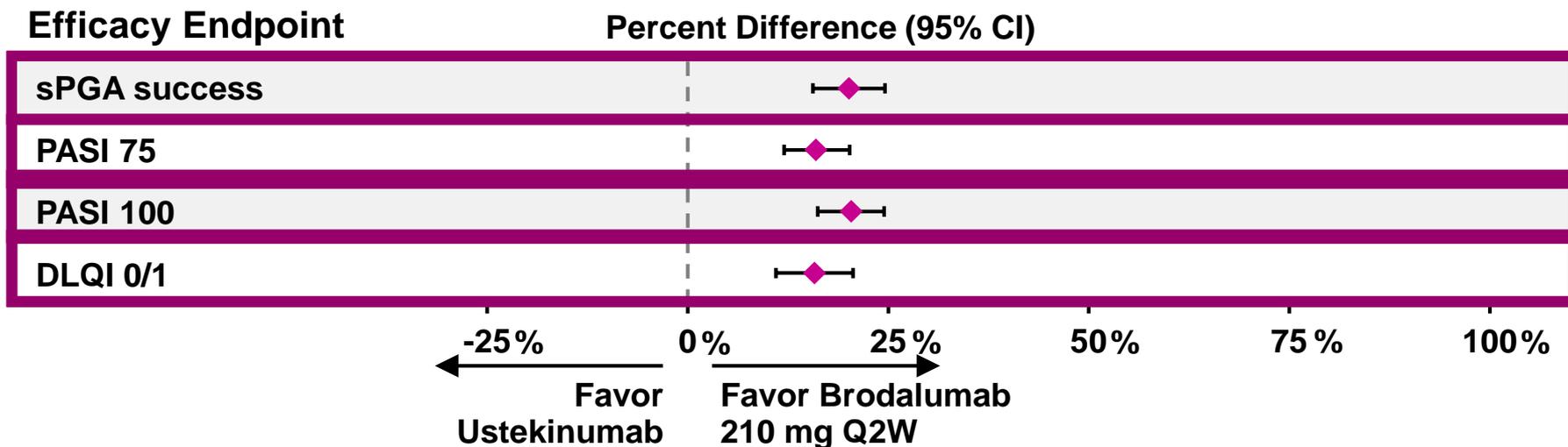
- **Worsening of Crohn's Disease**
- **Neutropenia**
- **Infections**

Rare events with high background incidence in patient population:

- **MACE**
- **SIB**

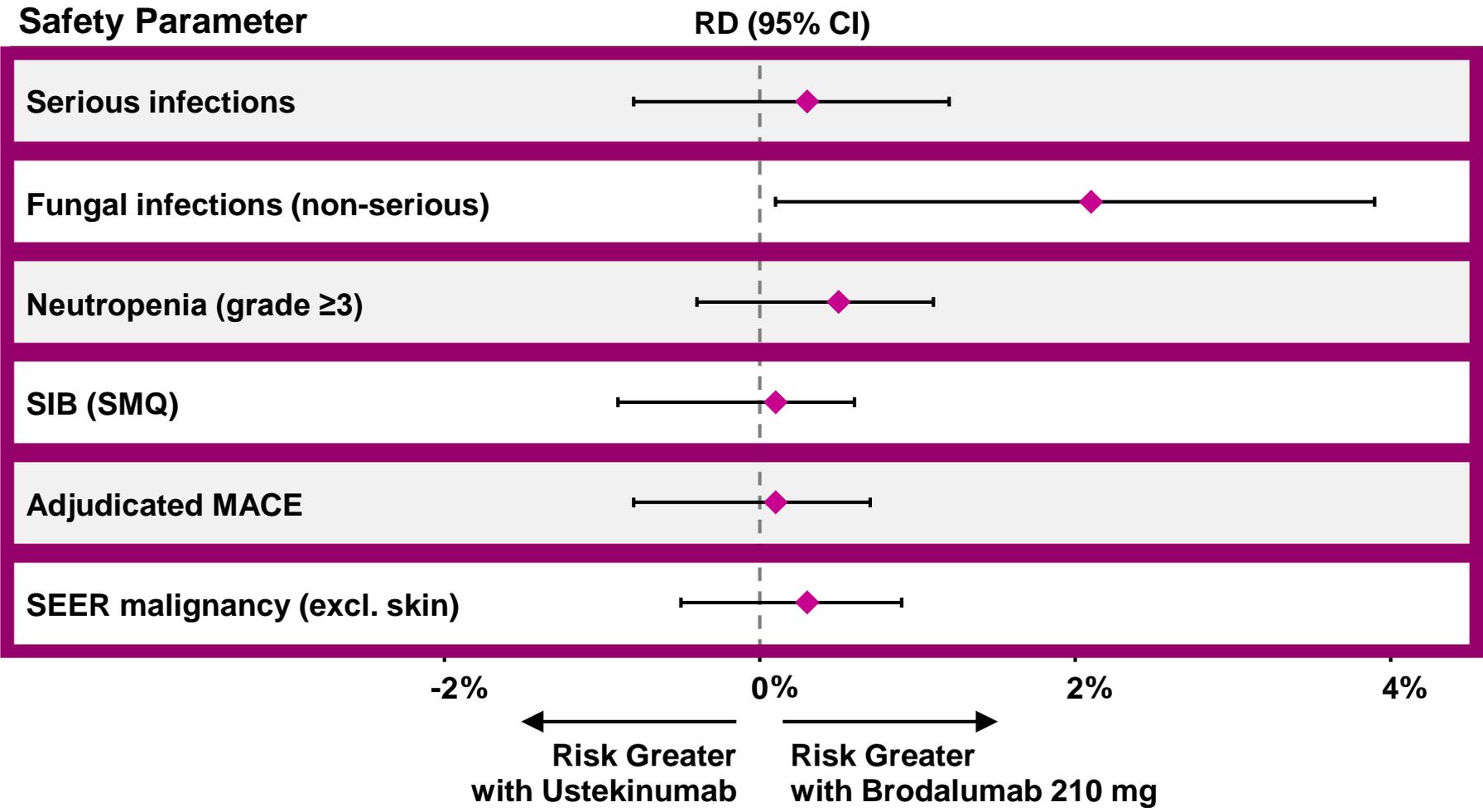
Benefit Risk Summary Plot

AMAGINE-2 and 3, Week 12



Risk Summary Plot

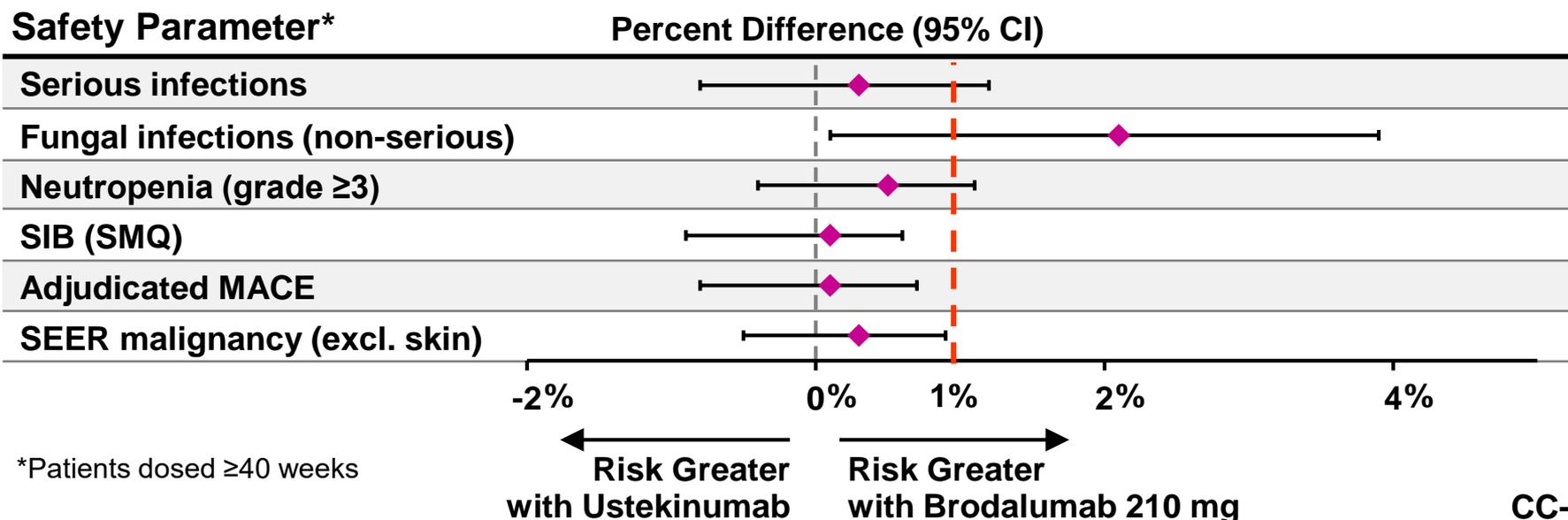
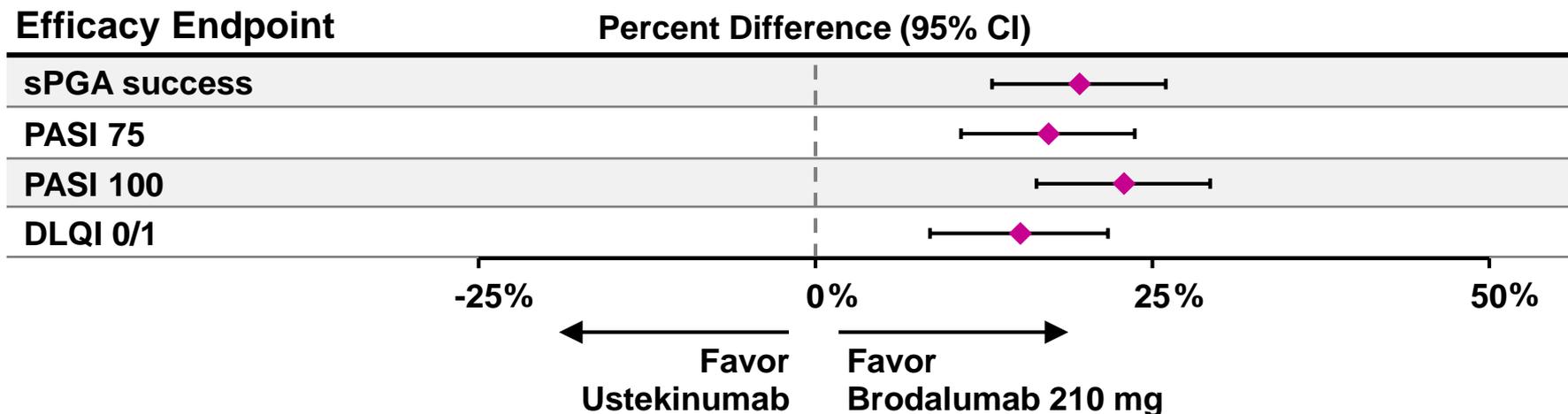
AMAGINE-2 and 3, Week 52



Data presented include patients dosed with ≥40 weeks therapy

Benefit Risk Summary Plot

AMAGINE-2 and 3, Week 52



*Patients dosed ≥40 weeks

Baseline BSA Involvement 92%



Benefit-Risk

Conclusion

Tage Ramakrishna, MD

Responders

Lori Davis, PhD

Associate Director of Biostatistical Consulting QST Consultations, Ltd.

- Dr. Davis is primarily responsible for the biostatistical methodology and development of scientific strategy for handling complex statistically focused challenges within clinical trial design, execution and reporting
- Dr. Davis has experience across a diverse range of therapeutic areas including but not limited to dermatology, neuroscience (schizophrenia, depression, ADHD), oncology, virology, vaccines and diabetes

Michele Hooper, MD, MS

Independent Consultant (Executive Director, Global Safety, Amgen, Retired)

- Dr. Hooper is a consultant in patient safety. Her career spans many years in academic rheumatology with an emphasis on clinical trials and ten years in industry in clinical development in the therapeutic area of Inflammation, including psoriasis and patient safety
- Dr. Hooper has published in the area of risk of malignancy in children and adults exposed to TNF blockers
- Dr. Hooper graduated from McGill Medical School in Montreal, Canada and completed fellowships in rheumatology (University of Virginia) and Allergy Immunology (University of Rochester)

Lauren B. Marangell, MD

- **Lauren B. Marangell, MD is president of Brain Health Consultants, a private consulting and psychiatric practice based in Houston, Texas.**
- **Marangell was previously the Brown Foundation Chair of Psychopharmacology of Mood Disorders and Professor of Psychiatry at Baylor College of Medicine.**
- **She has held research grants from the National Institute of Mental Health, NARSAD, the American Foundation for Suicide Prevention and Industry in areas related to mood, novel treatments and suicide.**
- **Served as a Chair for the Institutional Review Board that reviewed clinical research for all medical specialties for Baylor College of Medicine and Affiliated Hospitals**
- **Marangell was then recruited to Eli Lilly, where she served as a Distinguished Scholar in the area of neuroscience. This unique senior management position was designed to provide strategic guidance to compound development teams and medical affairs teams globally.**
- **Marangell received her medical degree at Baylor College of Medicine, completed her internship, residency, and chief residency at Albert Einstein College of Medicine/Montefiore Medical Center, and then spent three years at the National Institute of Mental Health as a Fellow and Senior Staff Fellow specializing in mood disorders research. She has received numerous awards, including the Exemplary Psychiatrist Award from the National Alliance for the Mentally Ill. She lectures and publishes widely, including over 100 peer review publications and several clinical textbooks. Her books have been translated into 4 languages, including Mandarin.**

Peter Kowey, MD

Professor of Medical and Clinical Pharmacology, Jefferson Medical College; Chief, Division of Cardiovascular Diseases, Main Line Health System, The William Wikoff Smith Chair in Cardiovascular Research, Lankenau Hospital and Medical Research Center

- Previously, Dr. Kowey was a Professor at the Medical College of Pennsylvania.
- He has been the recipient of over 150 grants, has authored or co-authored over 400 papers and scientific reports
- Dr. Kowey is a Fellow of the Clinical Council of the American Heart Association, the American College of Cardiology, the American College of Physicians, the College of Physicians of Philadelphia, the American College of Chest Physicians, and the American College of Clinical Pharmacology
- He was a founding member of the Philadelphia Arrhythmia Group and a charter member of the North American Society of Pacing and Electrophysiology
- He spent nine years as a member of the Cardio-Renal Drug Advisory Committee, four years on the Cardiovascular Devices Committee of the Food and Drug Administration, and was on the Expert Advisory Panel of the U.S. Pharmacopeial convention
- Dr. Kowey is a graduate of St. Joseph's University and the University of Pennsylvania School of Medicine, Philadelphia, Pennsylvania
- He completed his residency training in internal medicine at Penn State University and was a Fellow in cardiovascular medicine and research at the Harvard University School of Public Health, the Peter Bent Brigham Hospital, and the West Roxbury VA Hospital

Mark Lebwohl, MD

Professor and Chairman, Kimberly and Eric J Waldman Department of Dermatology Icahn School of Medicine at Mount Sinai

- Dr. Lebwohl has been practicing dermatology since 1983
- He is professor and chairman of the Department of Dermatology at The Mount Sinai School of Medicine
- Dr. Lebwohl has served as president of the New York Dermatological Society, the Manhattan Dermatologic Society, and the New York State Society of Dermatology, and as chairman of the Dermatology Section of the New York Academy of Medicine
- Dr. Lebwohl has served as chairman of the Psoriasis Task Force of the American Academy of Dermatology, and has directed the AAD's annual Psoriasis Symposium, Diagnostic Update Symposium and Therapeutics Symposium
- Dr. Lebwohl is chairman of the Medical Board of the National Psoriasis Foundation.
- He is the founding editor of Psoriasis Forum as well as medical editor of the bulletin of the National Psoriasis Foundation, Psoriasis Advance
- He is on the editorial board of the Journal of the American Academy of Dermatology and is editor of the Dermatology Section of Scientific American Medicine, now called ACP Medicine

Kim Papp, MD, PhD, FRCPC

Probity Medical Research, Inc.

- Dr. Kim Papp is a Member of the College of Physicians and Surgeons of Ontario, a Fellow of the Royal College of Physicians and Surgeons of Canada, and an American Board of Dermatology Diplomate
- The Waterloo, Ontario, Canada based dermatologist has over 20 years' experience as a Principal Investigator, and has conducted over 130 psoriasis studies in which he closely supervised and assessed over 2750 subjects
- Dr. Papp is an internationally renowned Key Opinion Leader in psoriasis research who conducts clinical trials on a wide range of dermatological disorders
- Dr. Papp, with the support of Probity Medical Research, an organization for which he serves as Founder and President, has earned the distinction of top enrolling investigator in over 70 international dermatology studies

Brodalumab

Dermatologic and Ophthalmic Drugs Advisory Committee

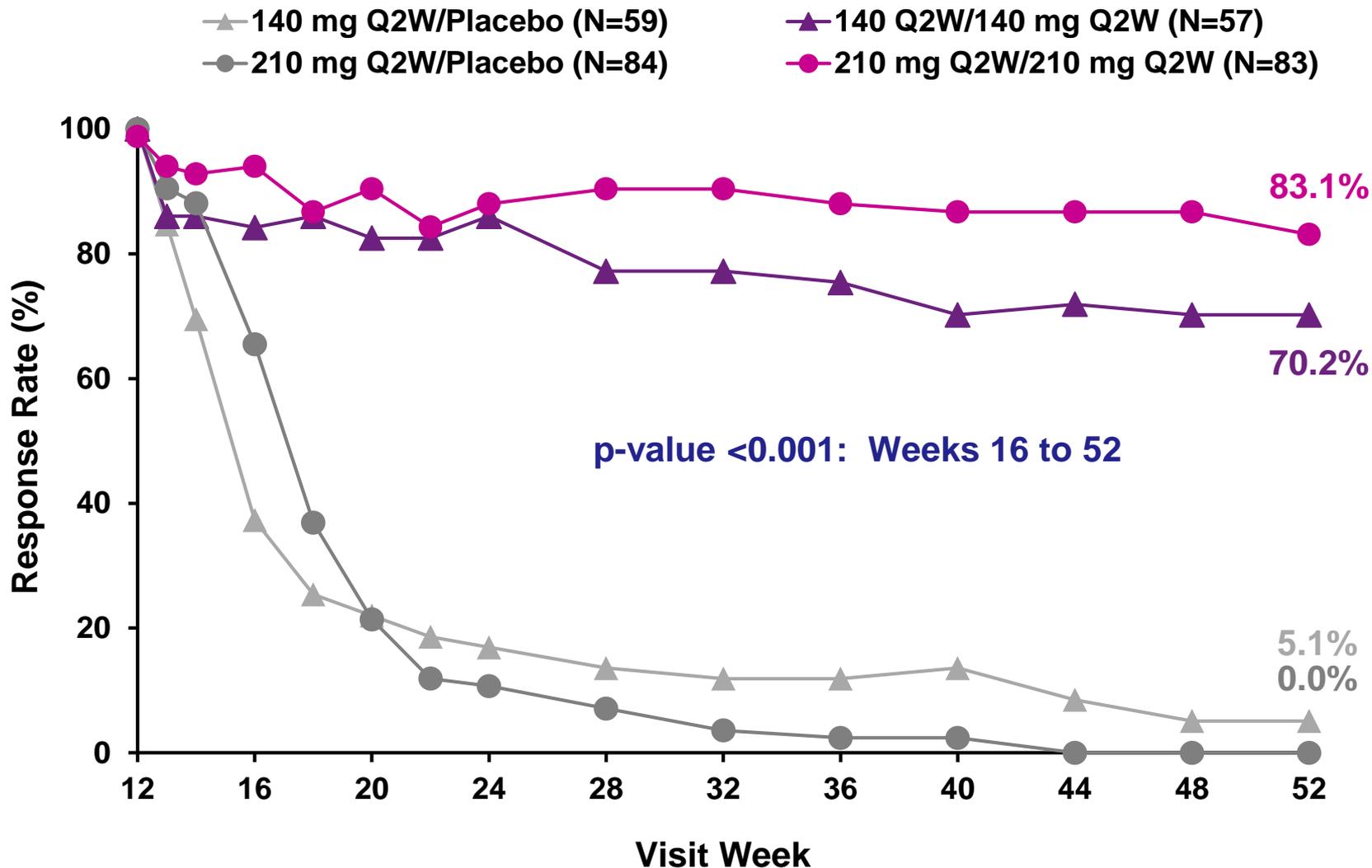


SPONSOR BACKUPS SHOWN

Brodalumab Has No Effect on C-Reactive Protein (CRP) Levels

	Brodalumab			
	Placebo N=313	Ustekinumab N=313	140 mg Q2W N=626	210 mg Q2W N=622
Baseline				
n	310	309	612	609
Median	2.71	2.78	2.65	2.74
Min, max	0.2, 96.6	0.2, 98.5	0.2, 250.0	0.2, 147.0
Change from Baseline				
n	294	298	583	585
Median	-0.08	-0.25	0.00	-0.16
Min, max	-84.0, 149.6	-73.6, 45.1	-170.9, 94.5	-124.8, 97.4

sPGA Success After Randomized Withdrawal (NRI) AMAGINE-1



Aggression, Impulsivity and Irritability in 52 Week Psoriasis Data

- **1 event of Grade 1 aggression and 1 event of Grade 1 impulsivity not associated with SIB**
- **6 events of irritability (4 Grade 1; 2 Grade 2)**
 - ▶ 2 not associated with SIB
 - ▶ Brodalumab:
 - ▶ 1 patient with suicide attempt had prior Grade 1 AE of irritability resolved before SIB event
 - ▶ 1 patient with suicide attempt had irritability during acute alcohol withdrawal
 - ▶ 1 patient with suicidal ideation and low grade irritability, had bipolar disorder, PTSD, depression, alcohol abuse, domestic and financial stressors
 - ▶ Ustekinumab:
 - ▶ 1 patient with history of suicidal ideation, bipolar disorder, depression, PTSD, anxiety, mood disorder, alcohol abuse developed suicidal ideation with associated irritability, depression and insomnia in association with marital and financial stressors

Exclusion Criteria for SIB Risk Factors in Psoriasis Programs

Secukinumab	Any psychiatric condition precluding adherence to the protocol; history or evidence of ongoing alcohol/drug abuse ^a
Apremilast	Clinically significant psychiatric disorder or active or recent (within 6 mo) substance abuse
Ixekizumab	Significant, uncontrolled neuropsychiatric disorder ; history of suicide attempt ; QIDS-SR16 score of ≥ 3 (ideation) ; at risk for suicide ^b
Ustekinumab	Severe, progressive or uncontrolled psychiatric disease
Brodalumab	Medical condition that could cause the study to be detrimental to the patient

clinicaltrials.gov; clinicaltrialsregister.eu;

^aProtocol for: Langley RG, Elewski BE, Lebwohl M, et al. Secukinumab in plaque psoriasis — results of two phase 3 trials. *N Engl J Med* 2014;371:326-38. DOI: 10.1056/NEJMoa1314258

^bSupplement to: Griffiths CEM, Reich K, Lebwohl M, et al, for the UNCOVER-2 and UNCOVER-3 investigators. Comparison of ixekizumab with etanercept or placebo in moderate-to-severe psoriasis (UNCOVER-2 and UNCOVER-3): results from two phase 3 randomized trials. *Lancet* 2015; published online June 10. [http://dx.doi.org/10.1016/S0140-6736\(15\)60125-8](http://dx.doi.org/10.1016/S0140-6736(15)60125-8).

SIB at 52 Week by Baseline Risk Factors

Psoriasis Studies, Follow-up-Adj.

Subgroups	Ustekinumab N=613		Brodalumab N=4019	
	Number of patients (PY)	Number with SIB n (r)	Number of patients (PY)	Number with SIB n (r)
Depression				
Yes	99 (81)	2 (2.5)	562 (485)	5 (1.0)
No	514 (423)	1 (0.2)	3457 (3062)	2 (0.1)
Suicidality				
Yes	27 (24)	2 (8.3)	102 (96)	1 (1.0)
No	507 (440)	0 (0.0)	3426 (3159)	2 (0.1)

Lamictal Warnings And Precautions

5.4 Suicidal Behavior and Ideation

Table 7 shows absolute and relative risk by indication for all evaluated AEDs

Indication	Placebo Patients with Events per 1,000 Patients	Drug Patients with events per 1,000 Patients	Relative Risk: Incidence of Events in Drug Patients/ Incidence in Placebo Patients	Risk Difference: Additional Drug Patients with Events per 1,000 Patients
Epilepsy	1.0	3.4	3.5	2.4
Psychiatric	5.7	8.5	1.5	2.9
Other	1.0	1.8	1.9	0.9
Total	2.4	4.3	1.8	1.9

Exclusion Criteria for Phase 3 PsA

- **Patient had a history or evidence of suicidal ideation (severity of 4 or 5) or any suicidal behavior based on an assessment with the electronic self-rated Columbia-Suicide Severity Rating Scale (eC-SSRS) at screening or at baseline**
- **Patient had a history or evidence of a psychiatric disorder or substance abuse that, in the opinion of the Investigator, would have posed a risk to patient safety or interfere with the study evaluation, procedures, or completion.**
- **Patient had severe depression based on a total score of ≥ 15 on the PHQ-8 at screening or baseline (note: patients with a total score of 10-14 on the PHQ-8 should have been referred to a mental health professional)**