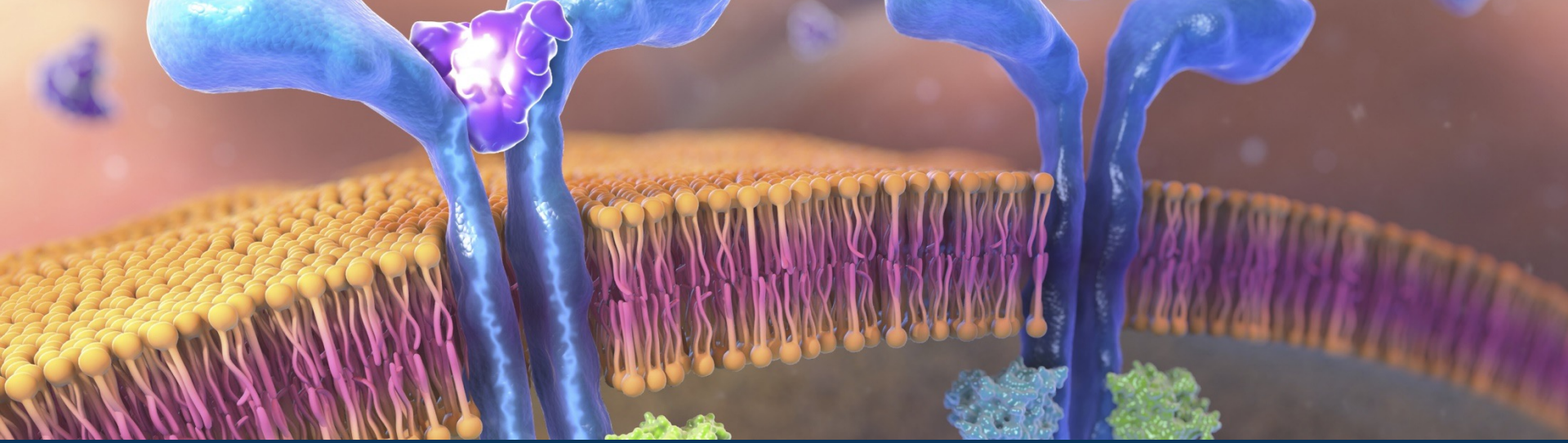

Taking Aim at the TYK2 Pathway in Psoriasis

Addressing Unmet Treatment and Patient Needs With an Innovative Therapeutic Approach

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Disclosures

Co-Chair/Planner

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Grant/Research Support from Bristol Myers Squibb; Dermavant Sciences, Inc.; Dermira, Inc.; Eli Lilly and Company; Leo Pharma Inc.; Pfizer Inc.; and UCB, Inc.

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Disclosures

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Seminar 1

A Closer Look at the Disease Burden and Unmet Treatment Needs in Psoriasis

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Signs and Symptoms of Psoriasis[1,2]

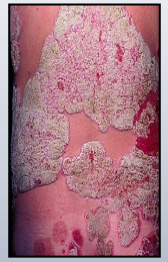
- Psoriasis is a chronic, immune-mediated disease, manifesting in skin symptoms that greatly impact patient quality of life
  - Affects >8 million Americans

- While patches of thickened, dry skin are common, psoriasis can cause many signs and symptoms; what patients see and feel tends to vary with the
  - Type of psoriasis present
  - Places psoriasis appears on the body
  - Amount of psoriasis a patient has

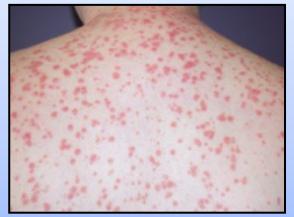
There are differences between patients' individual needs and their perception of psoriasis

1. https://www.psoriasis.org/about-psoriasis/. 2. https://www.aad.org/public/diseases/psoriasis/what/symptoms.

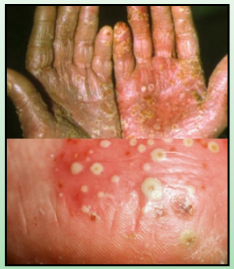
Major Subtypes of Psoriasis



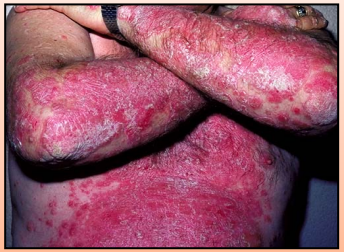
Chronic plaque psoriasis
(most common)



Guttate psoriasis



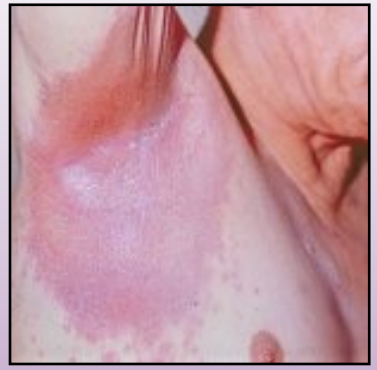
Pustular psoriasis

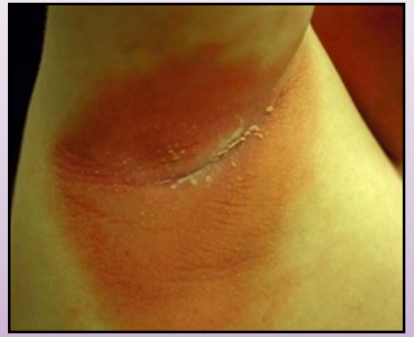


Erythrodermic psoriasis

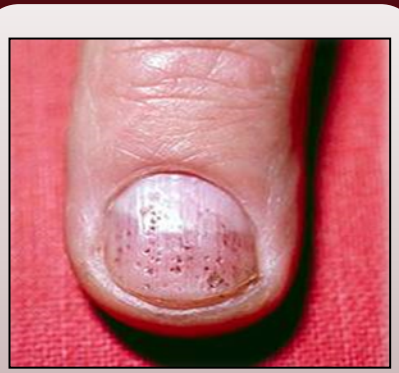
Special Sites: Inverse Psoriasis

- Characteristic findings include well-demarcated, smooth, shiny plaques with absent or minimal scale that are often misdiagnosed as intertriginous fungal or bacterial infections
- Presentation involving the intertriginous areas, including the inguinal, perineal, genital, intergluteal, axillary, or inflammatory regions

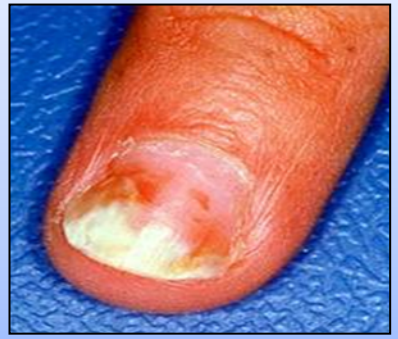




Special Sites: Nail Psoriasis



- Pitting

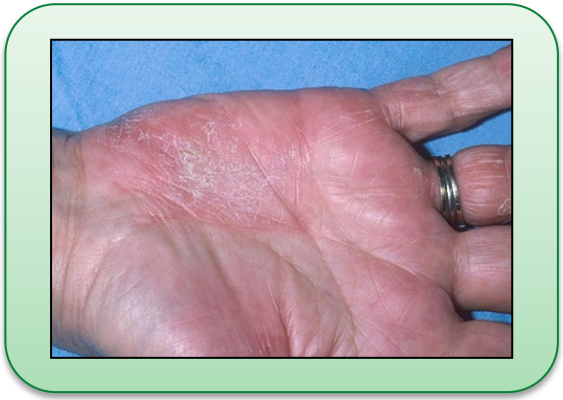


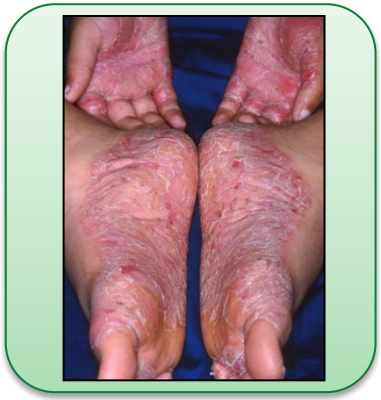
- Lifting of nail plate from nail bed (onycholysis)
- Red spots (salmon patches)

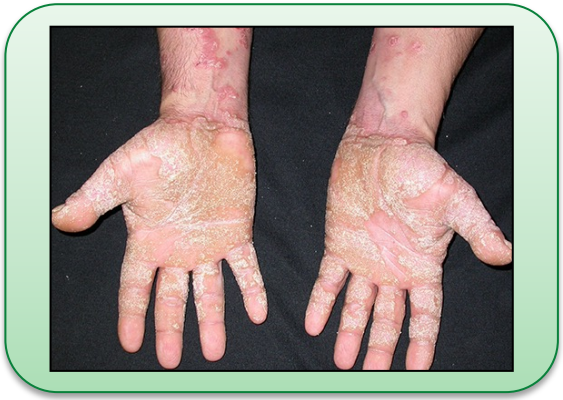
- Nail plate thickening
- Crusting under nail
- Nail plate crumbling

Special Sites: Palmoplantar Psoriasis

- Involves the palms or soles; classic presentation consists of erythematous, hyperkeratotic plaques that may have associated fissures
  - Fissures are often painful and may be disabling
  - Concomitant nail psoriasis is common
- Controversial whether palmoplantar pustulosis, a condition characterized by recurrent, pustular eruptions on the palms or soles, is a variant of psoriasis or a distinct disease entity

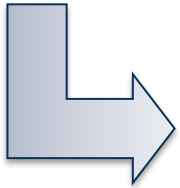






Classifying Psoriasis Severity[1]

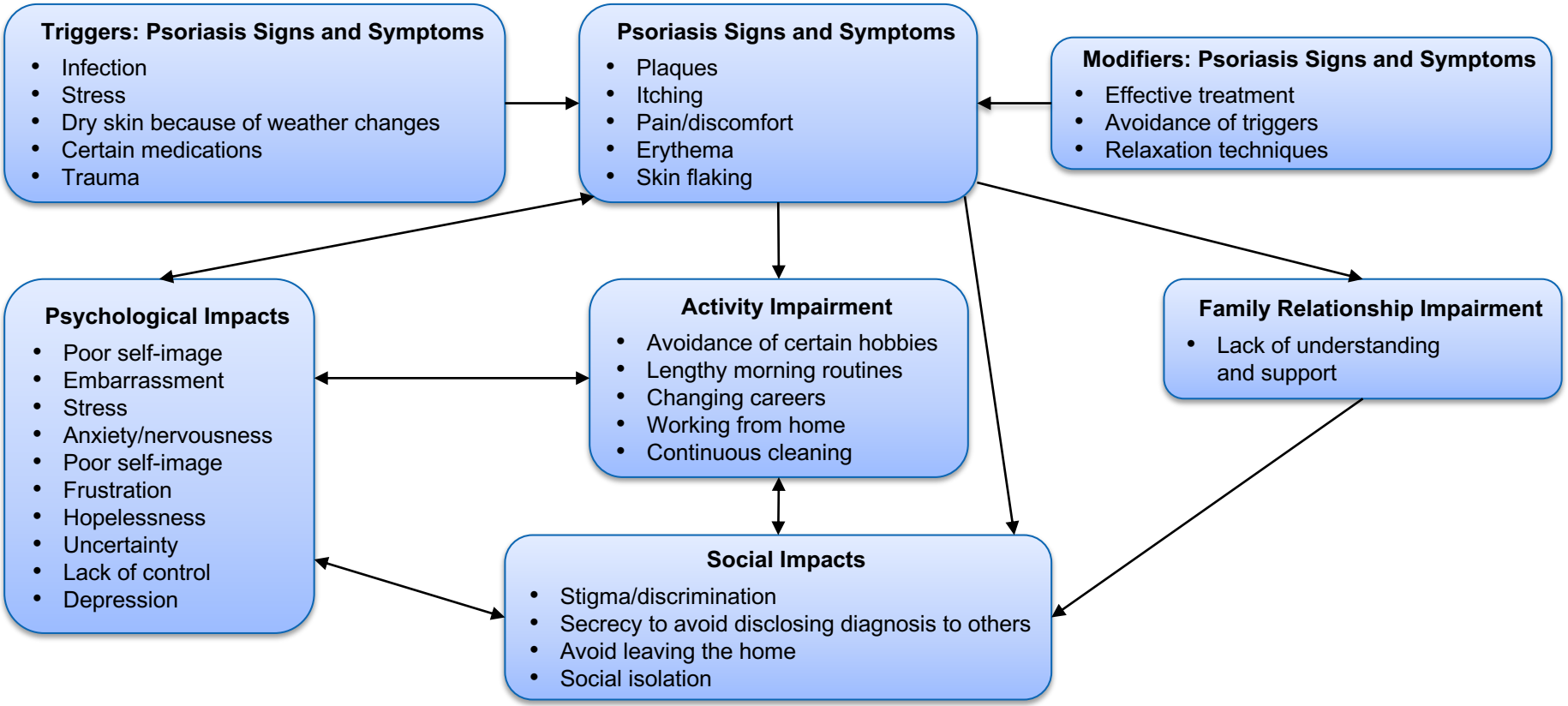
- Psoriasis severity is often categorized as mild, moderate, and severe, guided by measurements such as body surface area (BSA), Physician's Global Assessment (PGA), and the Psoriasis Area and Severity Index (PASI)
  - This may underestimate disease severity if lower degrees of skin involvement (eg, BSA <10%) are recorded, while ignoring disease involvement of "special areas" (eg, face, palms, soles, genitalia, scalp), prior treatment history, and/or the impact of psoriasis on quality of life



- In the recategorization of psoriasis severity, the Delphi consensus from the International Psoriasis Council said
  - "*Psoriasis patients should be classified as either candidates for topical therapy or candidates for systemic therapy; the latter are patients who meet at least one of the following criteria: 1) BSA >10%, 2) disease involving special areas, 3) failure of topical therapy*"

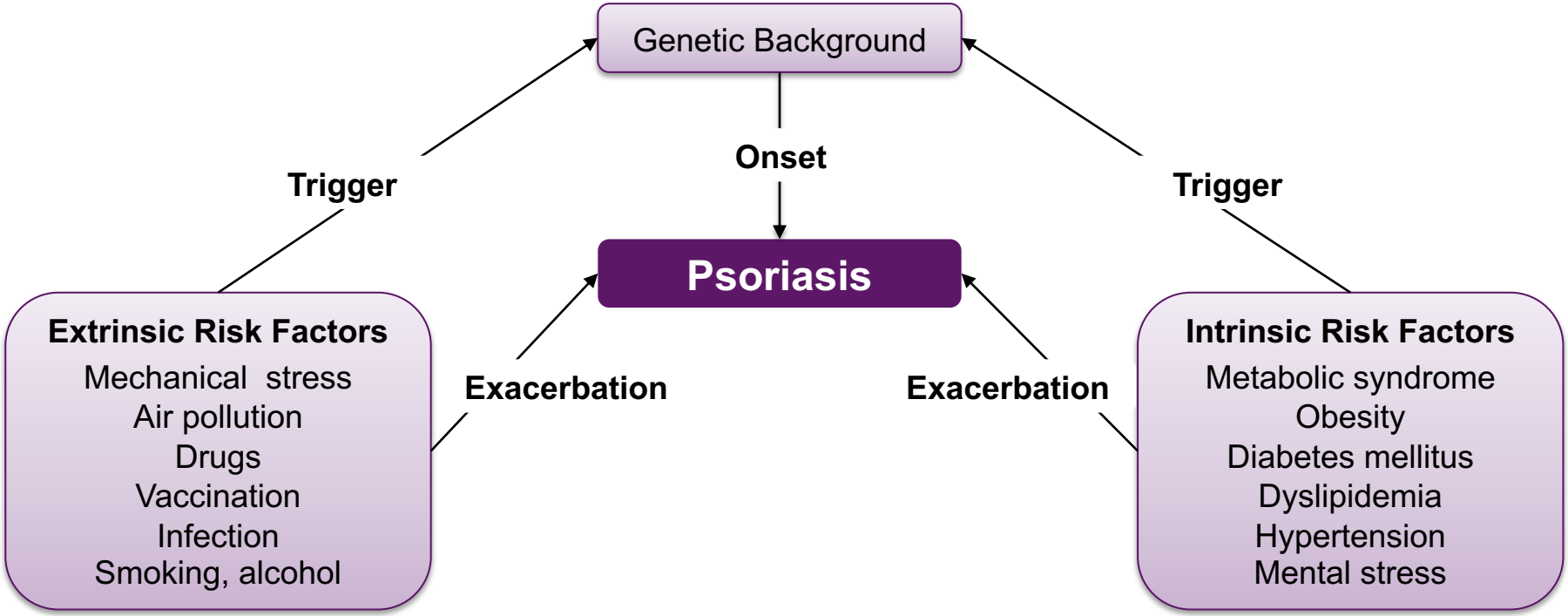
1. Strober B et al. *J Am Acad Dermatol*. 2020;82:117-122.

Patients With Psoriasis Have High Disease Burden[1]



1. Narayanan S et al. *Psoriasis (Auckl)*. 2014;5:1-7.

Risk Factors for the Onset and Exacerbation of Psoriasis[1]



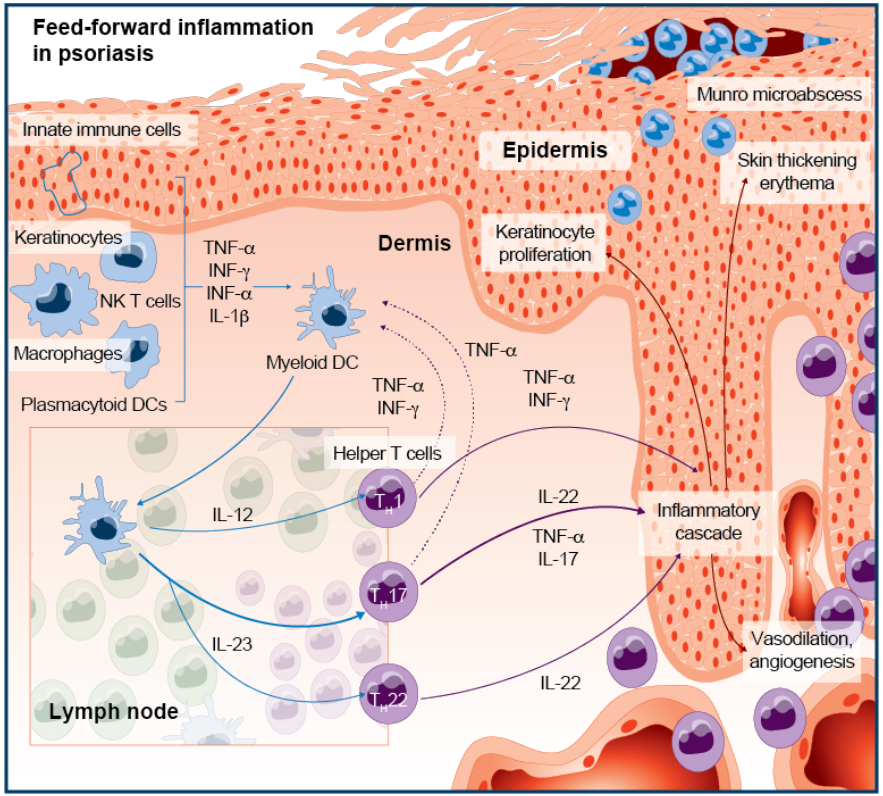
1. Kamiya K et al. *Int J Mol Sci*. 2019;20:4347.

Comorbidities Associated With Psoriasis[1]

Examples of Extracutaneous Disorders Linked to Psoriasis	
• Psoriatic arthritis	• Malignancy
• Cardiovascular disease	• Renal disease
• Metabolic syndrome	• Sleep apnea
• Mental health	• Chronic obstructive pulmonary disorder
• Lifestyle choices	• Uveitis
• Inflammatory bowel disease	• Hepatic disease

1. Elmets CA et al. *J Am Acad Dermatol*. 2019;80:1073-1113.

The IL-23/IL-17 Axis Plays a Central Role in the Immunopathogenesis of Psoriasis and Related Comorbidities[1-3]



1. Armstrong AW, Read C. *JAMA*. 2020;323:1945-1960. 2. Hawkes JE et al. *J Allergy Clin Immunol*. 2017;140:645-653.
3. Menter A et al. *Dermatol Ther (Heidelb)*. 2021;11:385-400.

Limitations of Biologic Therapies for Psoriasis[1]

Various biologic agents (eg, targeting TNF-α, IL-17, IL-23, and IL-12/23) have been developed for psoriasis

Treatment with these biologics is generally efficacious and well tolerated; however, there are limitations

- ❑ Some patients do not respond
- ❑ Some patients experience a loss of drug response during treatment
- ❑ It must be administered parenterally (IV or subcutaneous)
- ❑ There is risk of immunogenicity
- ❑ There are treatment-related expenses

1. Kvist-Hansen A et al. *Dermatol Ther (Heidelb).* 2020;10:29-42.

Overview of Small-Molecule Drugs for Psoriasis

- Can be administered orally or topically, with routes often associated with greater patient convenience, improved quality of life, and reduced healthcare costs[1]
- Conventional oral therapies (eg, acitretin, cyclosporine, methotrexate) are associated with various adverse events, drug–drug interactions, and long-term toxicity that require monitoring[1]
- Apremilast, a phosphodiesterase-4 inhibitor approved for moderate to severe psoriasis, provides limited efficacy and is poorly tolerated[2]

An unmet need exists for novel oral therapies that are safe and efficacious for psoriasis!

1. Nogueira M et al. *Drugs*. 2020;80:341-352. 2. Vangipuram R et al. *Expert Rev Clin Pharmacol*. 2017;10:349-360.

Seminar 2

JAK Inhibitors for the Treatment of Psoriasis: A Closer Look at the Evidence

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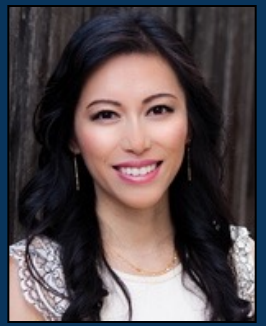

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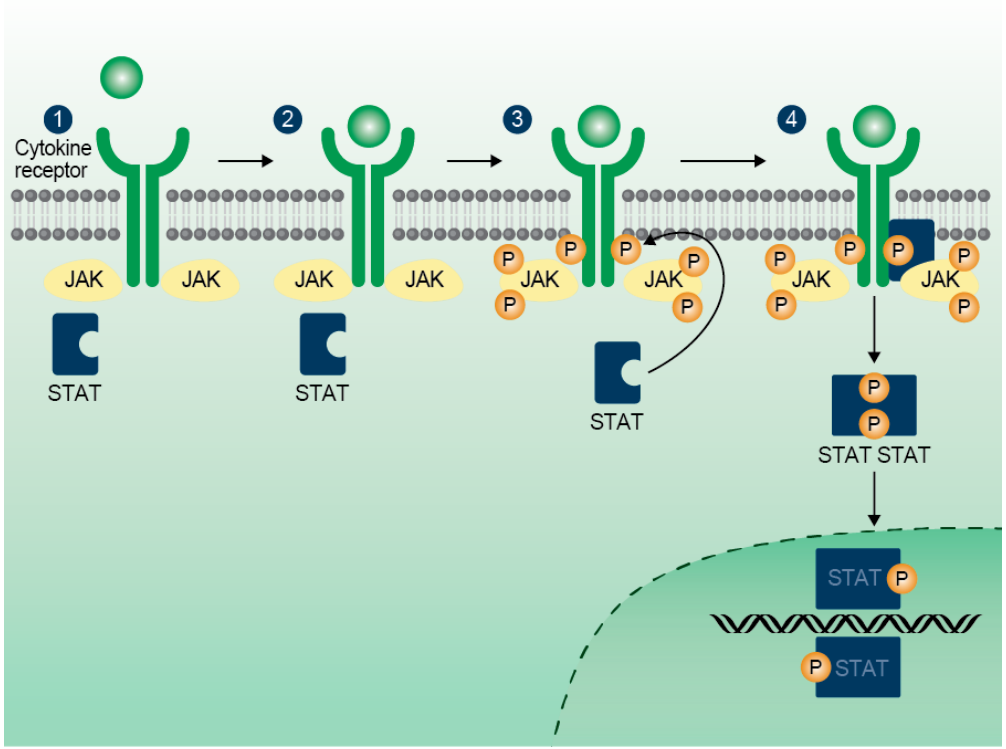
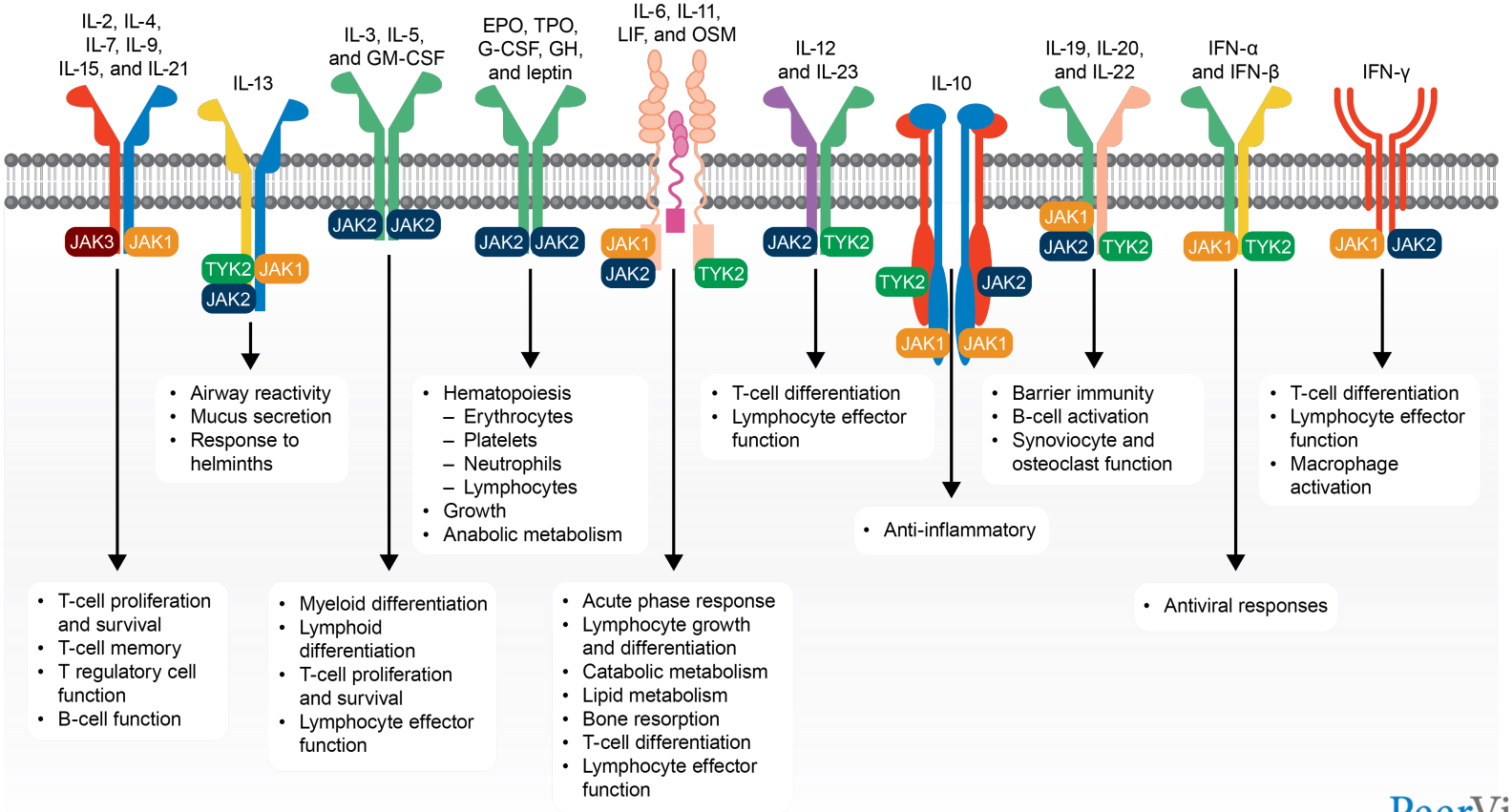
The JAK–STAT Pathway Is an Intracellular Signaling System Through Which Extracellular Factors Control Gene Expression[1]



1. Nogueira M et al. *Drugs.* 2020;80:341-352.

Effects of Targeting Different JAKs[1]



1. Schwartz DM et al. *Nat Rev Drug Discov*. 2017;17:78.

JAK Inhibitors for the Treatment of Psoriatic Disease: Current Status[1]

Drug	Main Sensitivity	Approved Indications	Phase of Clinical Trials in Plaque Psoriasis	Phase of Clinical Trials in Psoriatic Arthritis
Tofacitinib	JAK1 and JAK3	Rheumatoid arthritis Psoriatic arthritis Ulcerative colitis	Phase 3 (completed): not approved for psoriasis and no ongoing clinical trials	Already approved
Baricitinib	JAK1 and JAK2	Rheumatoid arthritis	Phase 2 (completed): no ongoing clinical trials	No clinical trials
Itacitinib	JAK1	None	Phase 2 (completed): no ongoing clinical trials	No clinical trials
Solcitinib	JAK1	None	Phase 2 (completed): discontinued investigation in psoriasis	No clinical trials
Abrocitinib	JAK1	None	Phase 2 (completed): discontinued investigation in psoriasis	No clinical trials
Filgotinib	JAK1	None	No clinical trials	Phase 3
Upadacitinib	JAK1	Rheumatoid arthritis	No clinical trials	Phase 3
Peficitinib	Pan-JAK (moderate selectivity for JAK3)	Rheumatoid arthritis (Japan)	Phase 2 (completed): discontinued investigation in psoriasis	No clinical trials

Boxed warning:
SERIOUS INFECTIONS, MORTALITY, MALIGNANCY AND THROMBOSIS

1. Nogueira M et al. *Drugs*. 2020;80:341-352.

JAK Inhibitors for the Treatment of Psoriatic Disease: Summary[1]

The inhibition of JAK family members can directly and indirectly suppress the activity of multiple cytokines that play a role in the pathogenesis of psoriasis

Differences are found between

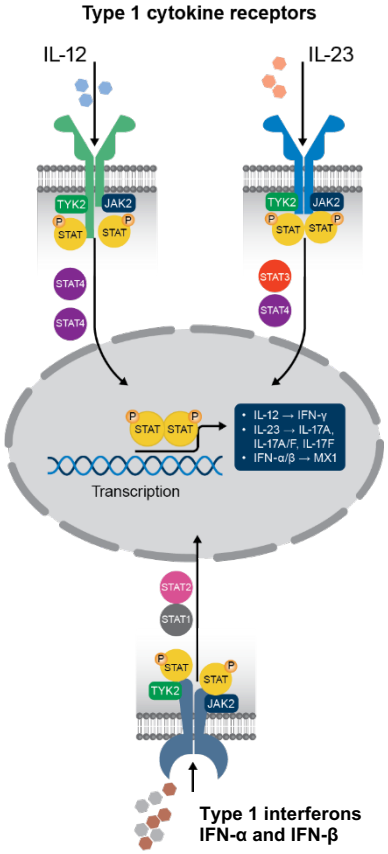
- Wide-ranging inhibition that suppresses the signaling of multiple psoriasis mediators
- Selective inhibition that can spare other members of the JAK family and thereby avoid corresponding safety concerns

Inhibition of JAK1, 2, and 3 has been associated with an increased risk of serious infections and opportunistic infections

- Dose-dependent changes in laboratory parameters (including lipids, levels of hemoglobin, decreased numbers of lymphocytes, NK cells, neutrophils, and platelets) have been observed, as well as cases of VTE and GI perforation

1. Nogueira M et al. *Drugs*. 2020;80:341-352.

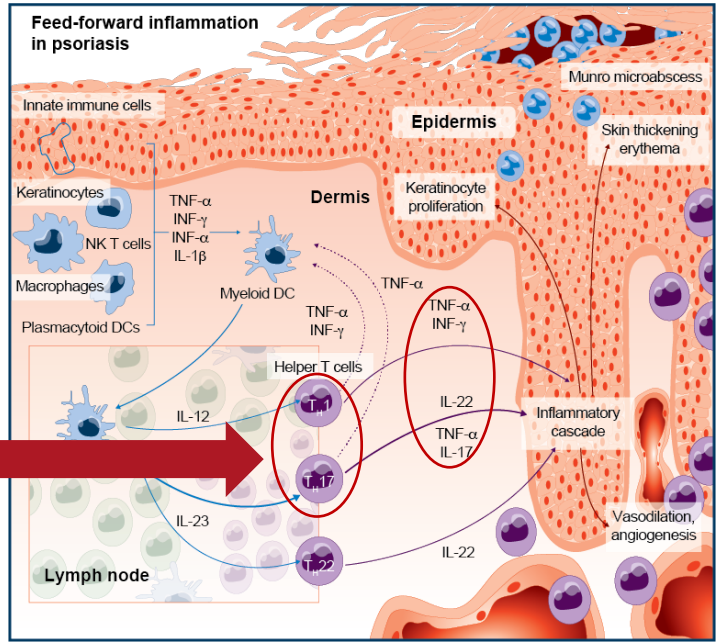
TYK2 Mediates Signaling and Functional Responses Downstream of the IL-12, IL-23, and Type 1 IFN Receptors[1]



1. Krueger JG et al. *J Am Acad Dermatol.* 2021;S0190-9622(21)02017-X.

TYK2 Pairs With JAK2 to Mediate Signal Transduction Pathways Downstream of IL-12 and IL-23 Receptors[1,2]

- IL-12 is essential for development of Th1 cells that release the proinflammatory cytokines tumor necrosis factor and IFN-γ
- IL-23 controls expansion and survival of Th17 cells
- Cytokines derived from Th1 and Th17 cells combined to amplify keratinocyte proliferation and activation



1. Krueger JG et al. *J Am Acad Dermatol.* 2021;S0190-9622(21)02017-X. 2. Armstrong AW, Read C. *JAMA*. 2020;323:1945-1960.

TYK2 Pairs With JAK1 to Mediate Signal Transduction Pathways Downstream of Type 1 IFN Receptors[1]

Type 1 IFNs

- Include IFN-α and IFN-β
- Are potent cytokines that are rapidly produced in large quantities by various cell types, especially plasmacytoid dendritic cells, during proinflammatory states such as viral infections
- Induce several powerful antiviral mechanisms, including the myxovirus resistance pathway
- Trigger vigorous proinflammatory effects important in psoriasis
  - Dendritic cell maturation and activation
  - Polarization of Th1 and Th17 cells
  - Reduction in regulatory T-cell function
  - Increased activation of B cells and associated antibody production

1. Krueger JG et al. *J Am Acad Dermatol.* 2021;S0190-9622(21)02017-X.

Rationale for TYK2 Inhibition as a Therapeutic Strategy in Psoriasis[1]

The TYK2 gene was first associated with psoriasis susceptibility in a genome-wide association study (GWAS) in 2010[2]

TYK2 loss-of-function mutation was associated with defects in several cytokine signaling pathways important in psoriasis pathogenesis[3]

Individuals with deactivating genetic variants of TYK2 were protected from some immune-mediated diseases; no ↑ risk of hospitalization because of mycobacterial, viral, or fungal infections[4]

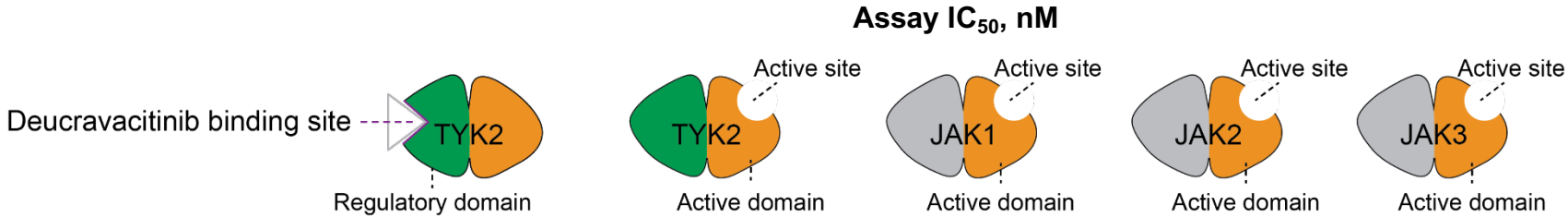
1. Nogueira M et al. *Drugs*. 2020;80:341-352. 2. Genetic Analysis of Psoriasis Consortium & the Wellcome Trust Case Control Consortium 2 et al. *Nat Genet*. 2010;42:985-990. 3. Minegishi Y et al. *Immunity*. 2006;25:745-755. 4. Dendrou CA et al. *Sci Transl Med*. 2016;8:363ra149.

TYK2 Inhibitors in Development for Moderate to Severe Psoriasis and PsA

Agent	MOA	Formulation	Disease
Deucravacitinib (BMS-986165)	TYK2 inhibitor (binds to the pseudokinase regulatory domain [allosteric inhibition])	Oral	PsO[a]
		Oral	PsA[b]
Brepocitinib (PF-06700841)	Dual TYK2/JAK1 inhibitor (binds to the active site in the catalytic domain)	Oral	PsO[a]
		Topical	PsO[c]
		Oral	PsA[b]
PF-06826647	TYK2 inhibitor (binds to the active site in the catalytic domain)	Oral	PsO[a]

[a] Moderate to severe disease. [b] Active disease. [c] Mild to moderate disease.

In-Vitro Data Suggest Differentiated Profile Versus JAK1-3 Inhibitors[1-3]

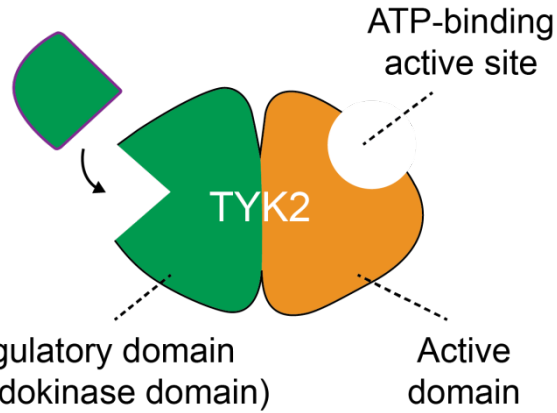


	Inhibitor	TYK2 Regulatory Domain	TYK2 Active Domain	JAK1	JAK2	JAK3
1	Tofacitinib	ND	489	15	77	55
2	Baricitinib	ND	61	4	7	787
3	Filgotinib	ND	2,600	363	2,400	>10,000
4	Upadacitinib	ND	4,690	47	120	2,304
5	Brepocitinib	ND	23	17	77	6,494
6	PF-06826647	ND	17	383	74	>10,000
7	**Deucravacitinib**	**0.2**	**>10,000**	**>10,000**	**>10,000**	**>10,000**

1. Wrobleski ST et al. *J Med Chem*. 2019;62:8973-8995. 2. Burke JR et al. *Sci Transl Med*. 2019;11:eaaw1736. 3. Winthrop KL. *Nat Rev Rheumatol*. 2017;13:234-243.

Deucravacitinib Targets a Novel Pseudokinase Domain, Which Offers Selective Inhibition of IL-23, IFN-α, and IL-12

Deucravacitinib



Cellular IC_{50}, nM[1]

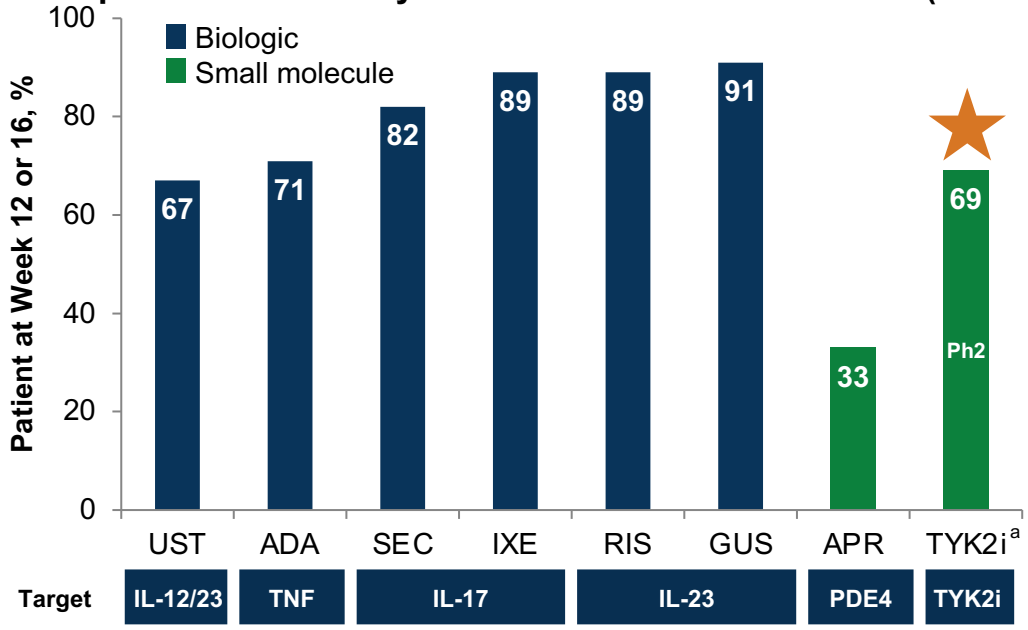
	IL-23	IFN-α	IL-12	EPO
Agent	TYK2/ JAK2	TYK2/ JAK1	JAK1/ JAK3	JAK2
Deucravacitinib	8	5	623	>10,000

1. Gillooly K et al. 2016 American College of Rheumatology/Association of Rheumatology Health Professionals Annual Meeting. Abstract 11L.

Deucravacitinib has Demonstrated Proof of Concept for TYK2 Inhibition in Psoriasis[1,2]

- Randomized, double-blind, placebo-controlled trial in adults with moderate to severe psoriasis (N = 267), excluding patients with a previous lack of response to agents targeting cytokine signaling through the same tyrosine kinase pathway

Response Rate for Key Products From Phase 3 Trials (PASI 75)



Phase 2 Takeaways

Robust Clinical Efficiency

- Consistent dose response with sustained efficiency after discontinuation of dosing
- Efficacy in both biologic-naïve and biologic-exposed subjects

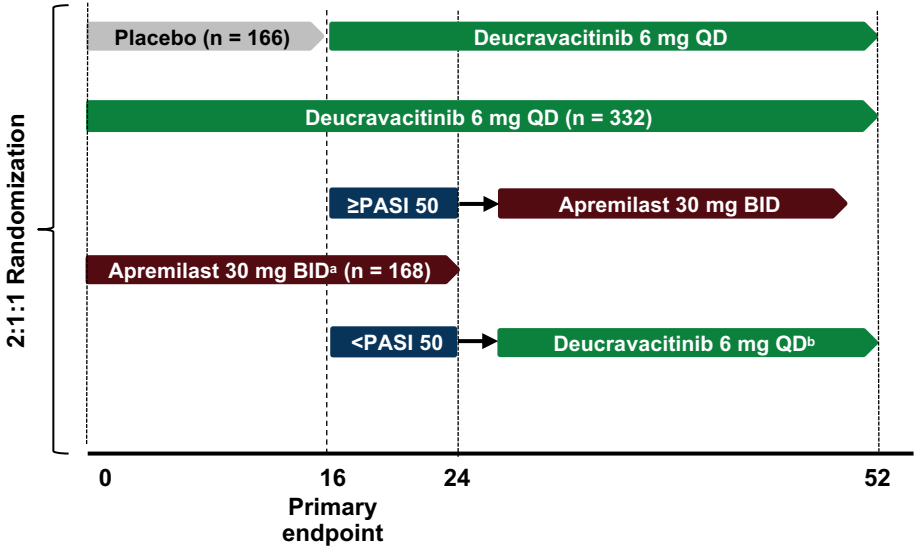
Validation of Target and Mechanism of Action

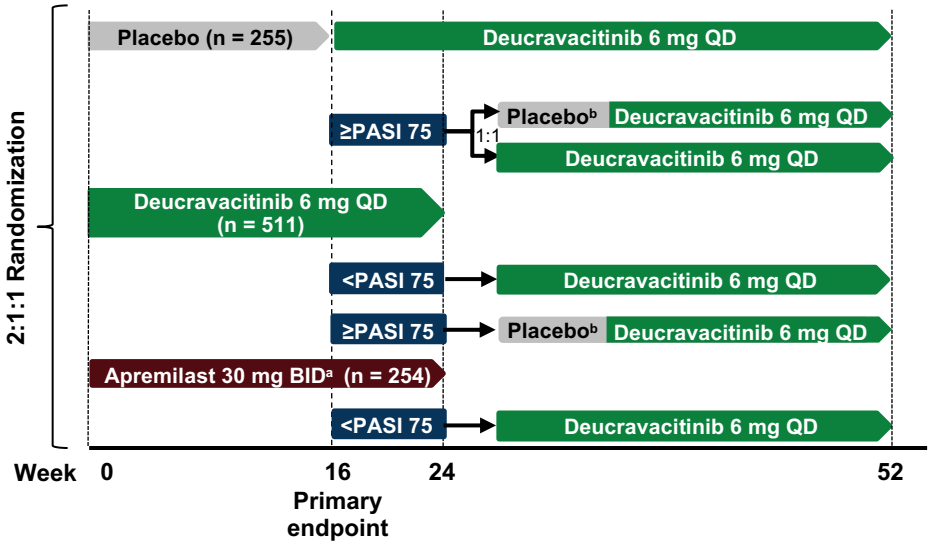
- Reduction in expression of genes of the IL-23/IL-12 and type 1 IFN pathways
- No change in JAK1, JAK2, or JAK3 biomarkers
- No dyslipidemia, liver abnormalities, lymphopenia, or thrombotic events associated with JAK inhibitors

[a] TYK2i data are from phase 2, 3 mg twice a day.

1. Papp K et al. *N Engl J Med*. 2018;379:1313-1321. 2. Krueger JG et al. 2018 Annual Congress of the European Academy of Dermatology and Venereology Congress.

Deucravacitinib: POETYK PSO-1 and PSO-2, Global Phase 3 Study Designs[1]





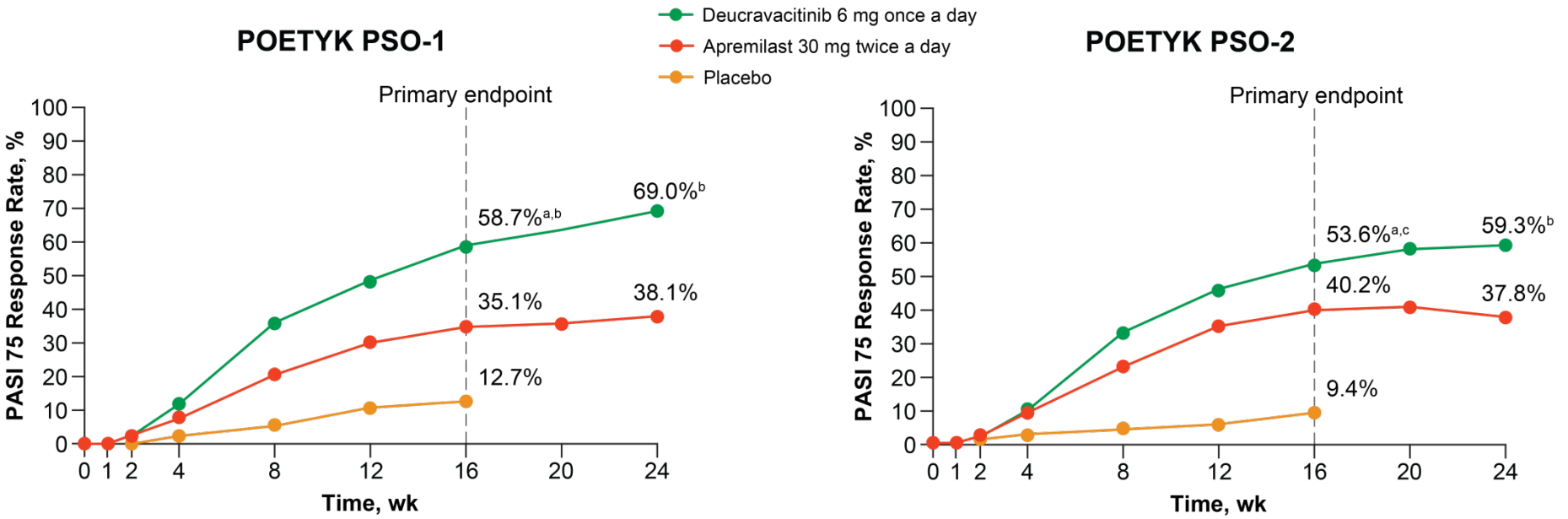
- Key eligibility criteria
  - Adults with moderate to severe plaque psoriasis
  - PASI ≥12, sPGA ≥3, BSA ≥10%
- Stratified by geographic region, body weight, and prior biologic use
- 92.5% of patients in PSO-1 and 89.4% in PSO-2 completed 16 weeks of deucravacitinib treatment vs 87.9% and 83.5%, respectively, for placebo, and 86.3% and 85.4%, respectively, for apremilast
- All patients were eligible for a long-term extension study after 52 weeks of treatment

Coprimary endpoints, deucravacitinib vs placebo at week 16
- **PASI 75**
- **sPGA 0/1**

[a] Apremilast was titrated from 10 mg once a day to 30 mg twice a day over the first 5 days of dosing.
[b] Upon relapse (≥50% loss of week 24 PASI percent improvement from baseline), patients were switched to deucravacitinib 6 mg once a day.

1. Armstrong A et al. 2021 Academy of Dermatology Virtual Meeting Experience (2021 AAD VMX).

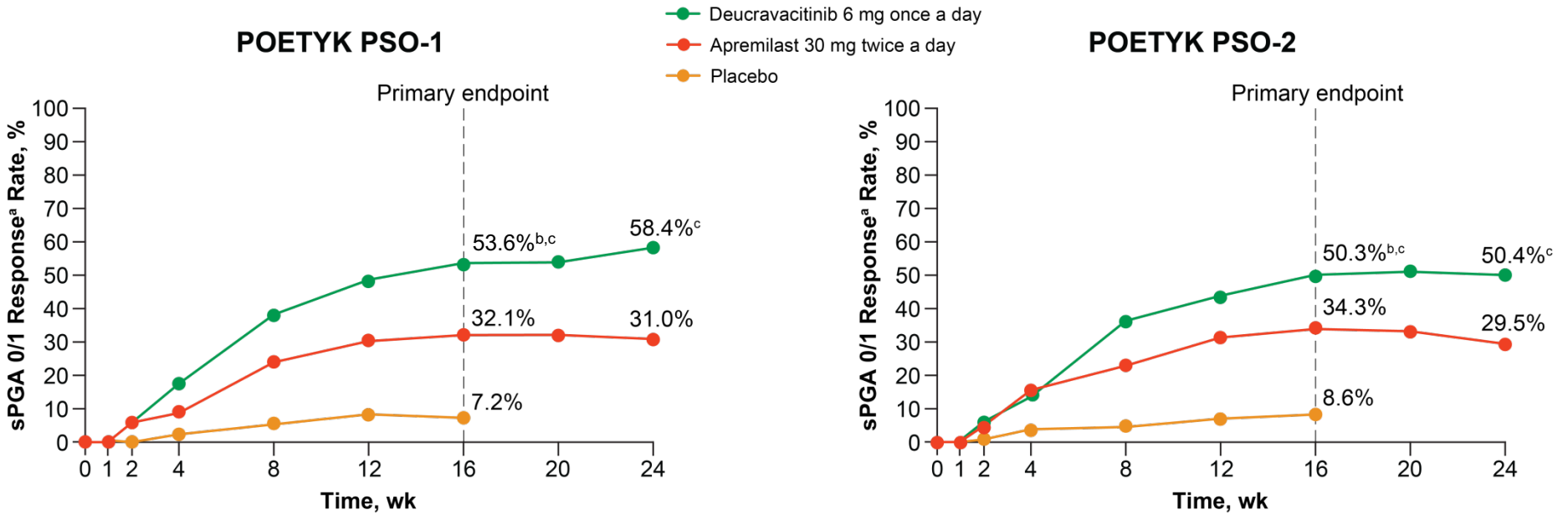
Significantly Greater Proportions of Patients in the Deucravacitinib Versus Placebo and Apremilast Arms Achieved PASI 75[1]



Durable response for deucravacitinib patients achieving PASI 75 at week 24
82.5% and 81.4%, respectively, maintained response at week 52

[a] $P < .0001$ vs placebo. [b] $P < .0001$ vs apremilast. [c] $P = .0003$ vs apremilast.
1. Armstrong A et al. 2021 AAD VMX.

Significantly Greater Proportions of Patients in the Deucravacitinib Versus Placebo and Apremilast Arms Achieved sPGA 0/1[1]



[a] Response defined as sPGA score of 0 or 1 with ≥2-point improvement from baseline. [b] $P < .0001$ vs placebo. [c] $P < .0001$ vs apremilast.

1. Armstrong A et al. 2021 AAD VMX.

POETYK PSO-1 and PSO-2: Coprimary and Secondary Endpoints[1]

Comparisons vs Placebo

Rank	Endpoint vs Placebo	PSO-1	PSO-2
1	PASI 90 at week 16[b]	✓	✓
2	ss-PGA 0/1 (BL ≥3) at week 16	✓	✓
3	sPGA 0 at week 16	✓	✓
4	PASI 100 at week 16[c]	✓	✓
5	PSSD Symptom Score 0 (BL ≥1) at week 16	✓	✓
6[a]	DLQI 0/1 (BL ≥2) at week 16	✓	✓
7[a]	Time to relapse until week 52 for week 24 PASI 75 responders	N/A	✓
8	PGA-F 0/1 (BL ≥3) at week 16	×	×

Comparisons vs Apremilast

Rank	Endpoint vs Apremilast	PSO-1	PSO-2
1	sPGA 0/1 at week 16	✓	✓
2	PASI 75 at week 16	✓	✓
3	PASI 90 at week 16[b]	✓	✓
4	sPGA 0/1 at week 24	✓	✓
5	PASI 75 at week 24	✓	✓
6	PASI 90 at week 24[d]	✓	✓
7	CFB PSSD Symptom Score at week 16	✓	✓
8	ss-PGA 0/1 (BL ≥3) at week 16	✓	✓
9	sPGA 0/1 at week 52 and week 24	✓	N/A
10	PASI 75 at week 52 and week 24	✓	NA
11	PASI 90 at week 52 and week 24	✓	N/A
12	sPGA 0 at week 16	✓	✓
13	PSSD Symptom Score of 0 at week 16 (BL ≥1)	×	×

Effectiveness shown across endpoints meaningful to patients

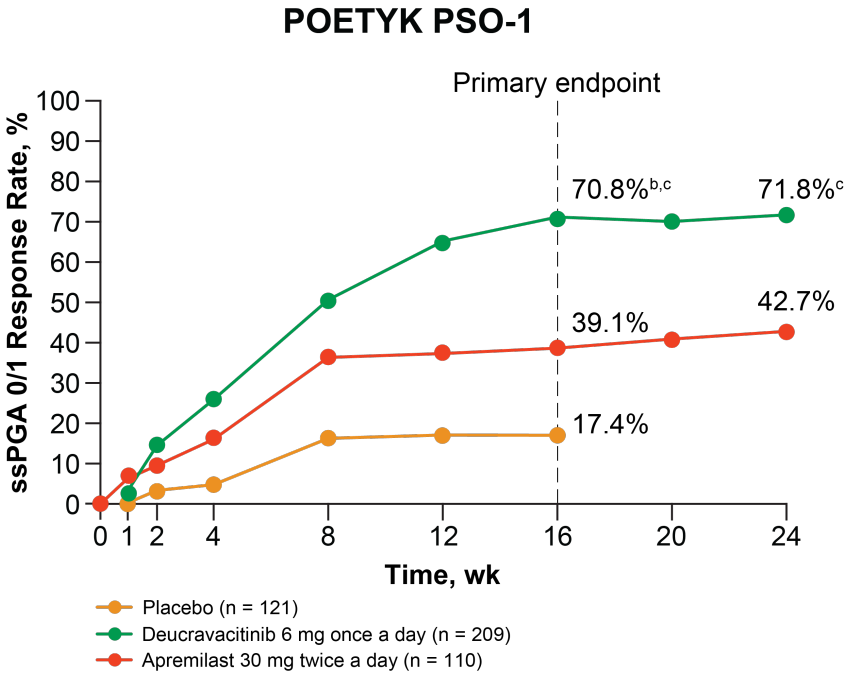
- Deep responses for skin clearance
- Hard-to-target areas (eg, scalp)
- Maintenance of response over time
- Quality of life

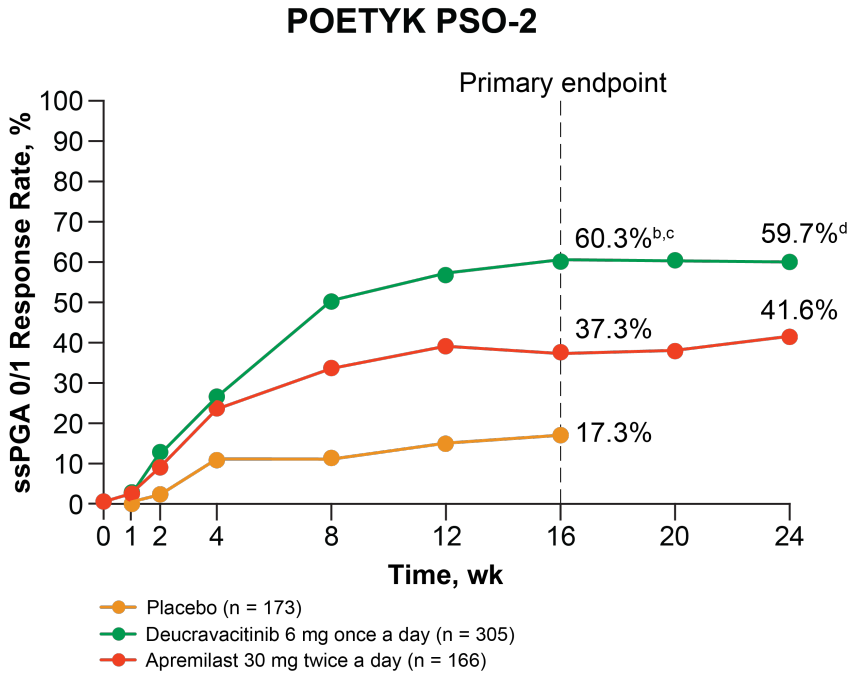
✓ Statistical significance achieved (all $P \leq .006$)
× Statistical significance not achieved (all $P \geq .062$)

[a] Ex-US hierarchy only. [b] PASI 90 at week 16 (PSO-1, PSO-2) = 35.8%, 27.2%.
[c] PASI 100 at week 16 (PSO-1, PSO-2) = 14.2%, 10.2%. [d] PASI 90 at week 24 (PSO-1, PSO-2) = 42.2%, 32.7%.

1. Armstrong A et al. 2021 AAD VMX.

Significantly Greater Proportions of Patients in the Deucravacitinib vs Placebo and Apremilast Arms Achieved an ss-PGA Score of 0/1 Response at Week 16[1,a]

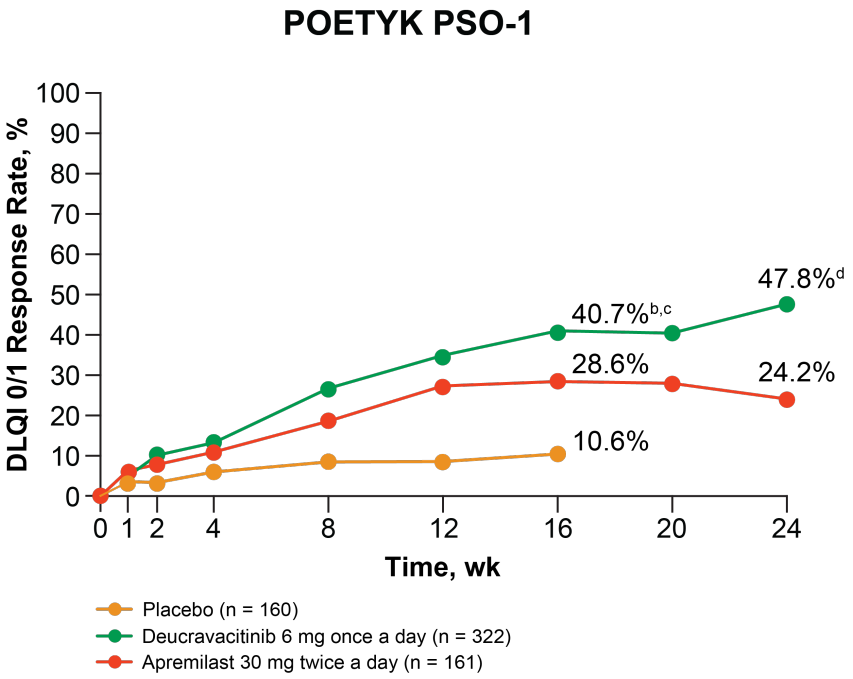


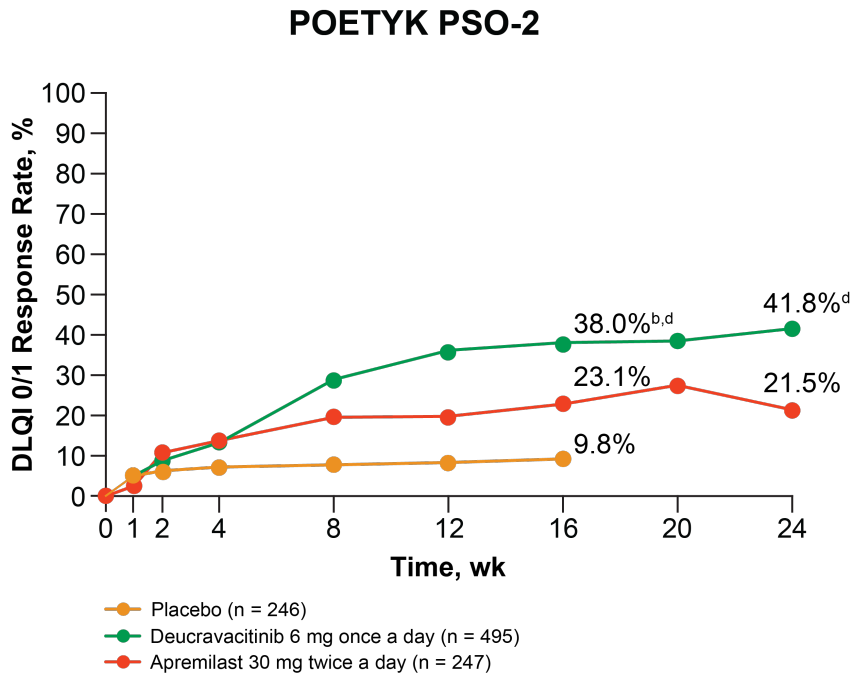


[a] Included patients with a baseline ss-PGA score ≥3. [b] $P < .0001$ vs placebo. [c] $P < .0001$ vs apremilast. [d] $P = .0002$ vs apremilast.

1. Armstrong A et al. 2021 AAD VMX.

Significantly Greater Proportions of Patients in the Deucravacitinib vs Placebo and Apremilast Arms Achieved DLQI 0/1 at Week 16[1,a]





[a] Among patients with baseline DLQI score ≥2. [b] $P < .0001$ vs placebo. [c] $P = .0106$ vs apremilast. [d] $P < .0001$ vs apremilast.

1. Armstrong A et al. 2021 AAD VMX.

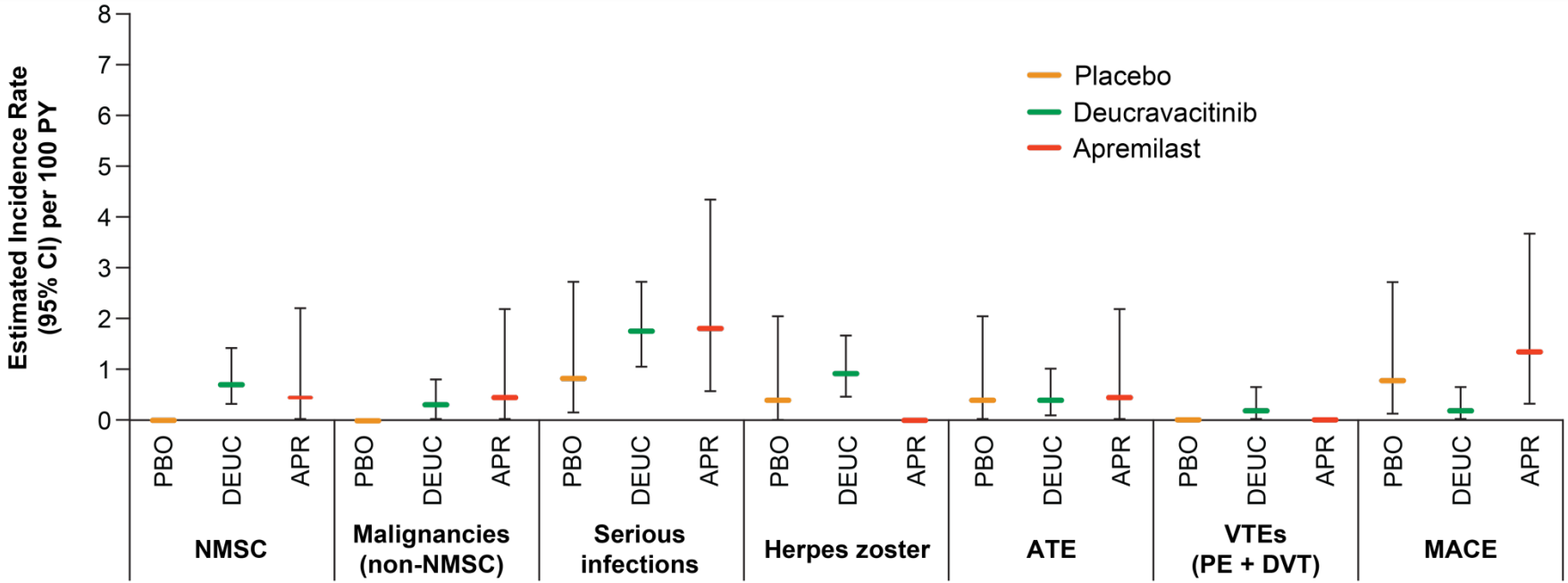
POETYK PSO-1 and PSO-2: Safety Summary, Weeks 0-52[1]

AE Category, n,[a] Exposure-Adjusted Incidence Rate (EAIR) Events per 100 Patient-Years (PY)	POETYK Integrated Safety (PSO-1 and PSO-2)		
	Placebo (n = 666; total PY, 240.9)	Deucravacitinib (n = 1,364; total PY, 969.0)	Apremilast (n = 422; total PY, 221.1)
Any AEs	347, **217.9**	995, **229.2**	299, **281.1**
Serious AEs	14, **5.7**	55, **5.7**	9, **4.0**
AEs leading to discontinuation	23, **9.4**	43, **4.4**	26, **11.6**
Deaths	1	2[b]	1
Most common AEs (≥5%) in any active treatment group			
Nasopharyngitis	54, **22.9**	229, **26.1**	54, **25.9**
Upper respiratory tract	33, **13.6**	124, **13.4**	27, **12.4**
Headache	21, **8.6**	80, **8.5**	53, **26.0**
Diarrhea	28, **11.6**	69, **7.3**	54, **26.5**
Nausea	10, **4.1**	20, **2.1**	47, **22.9**

- Per each study design, patients receiving placebo switched to deucravacitinib at week 16, and patients receiving apremilast failing to meet study-specific efficacy thresholds (PASI 50 in PSO-1, PASI 75 in PSO-2) switched to deucravacitinib at week 24
- Skin events of interest: folliculitis and acne
  - Folliculitis 2.0% (EAIR, **2.8**), and acne 2.1% (EAIR, **2.9**) with deucravacitinib
  - All cases were mild to moderate; one patient with folliculitis discontinued deucravacitinib treatment
- No new safety signals observed during weeks 16-52

[a] Includes AEs between first dose and 30 days following last dose or rollover to long-term extension.
[b] One additional death between weeks 16-52 because of hepatocellular carcinoma in a patient with a history of HCV infection and liver cirrhosis.
1. Armstrong A et al. 2021 AAD VMX.

No AEs of Interest Associated With JAK1-3[1,a]

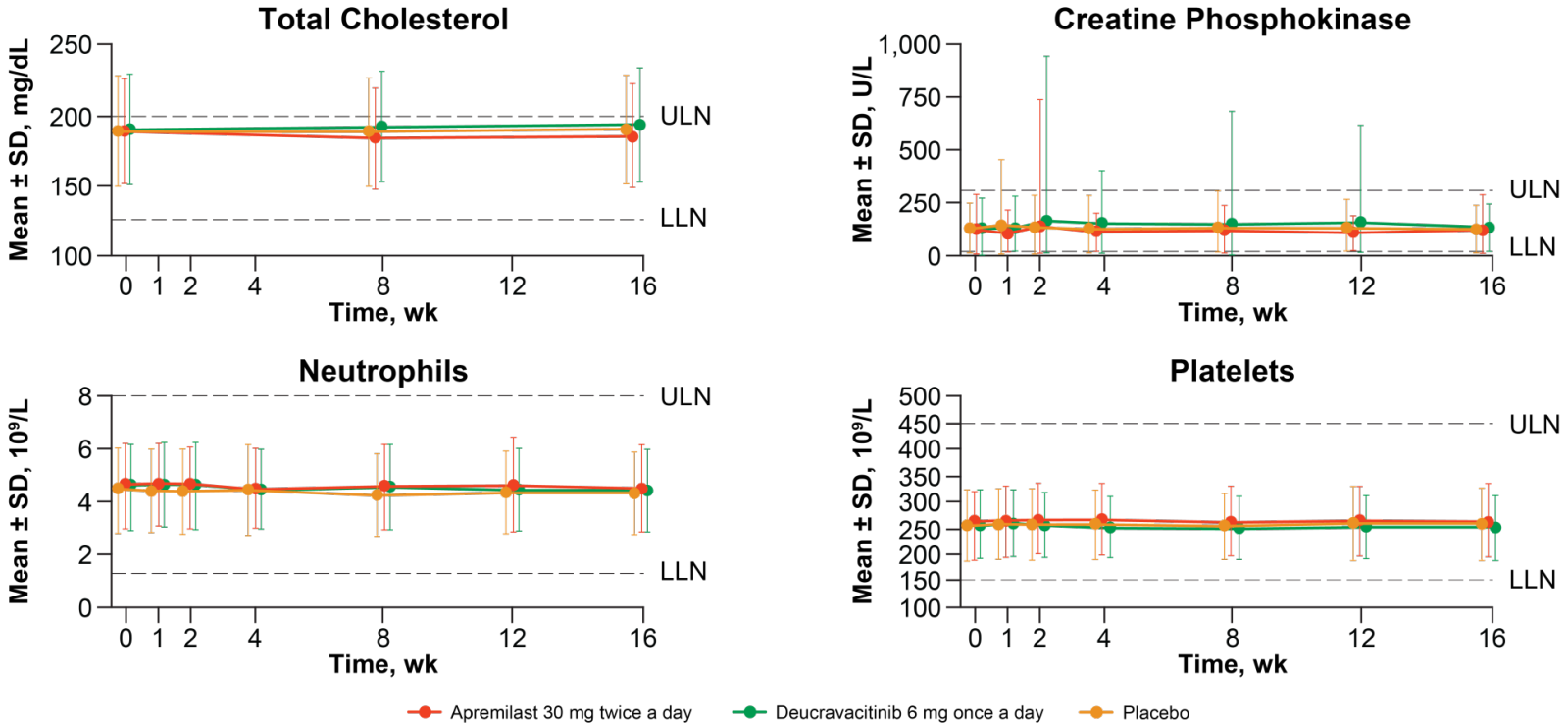


- None of the serious infections with deucravacitinib led to discontinuation
- No cases of herpes zoster with deucravacitinib were serious or systemic, and none led to discontinuation
- No tuberculosis events or opportunistic systemic infections were reported with deucravacitinib
- One SAE adjudicated as a VTE occurred in a patient receiving deucravacitinib who had an aortic dissection complicated by a PE

[a] Total exposure: deucravacitinib, 969.0 PY; placebo, 240.9 PY; apremilast, 221.1 PY. Most placebo-related data were obtained during weeks 0-16.

1. Armstrong A et al. 2021 AAD VMX.

No Clinically Significant Trends Were Observed for Laboratory Parameters[1]



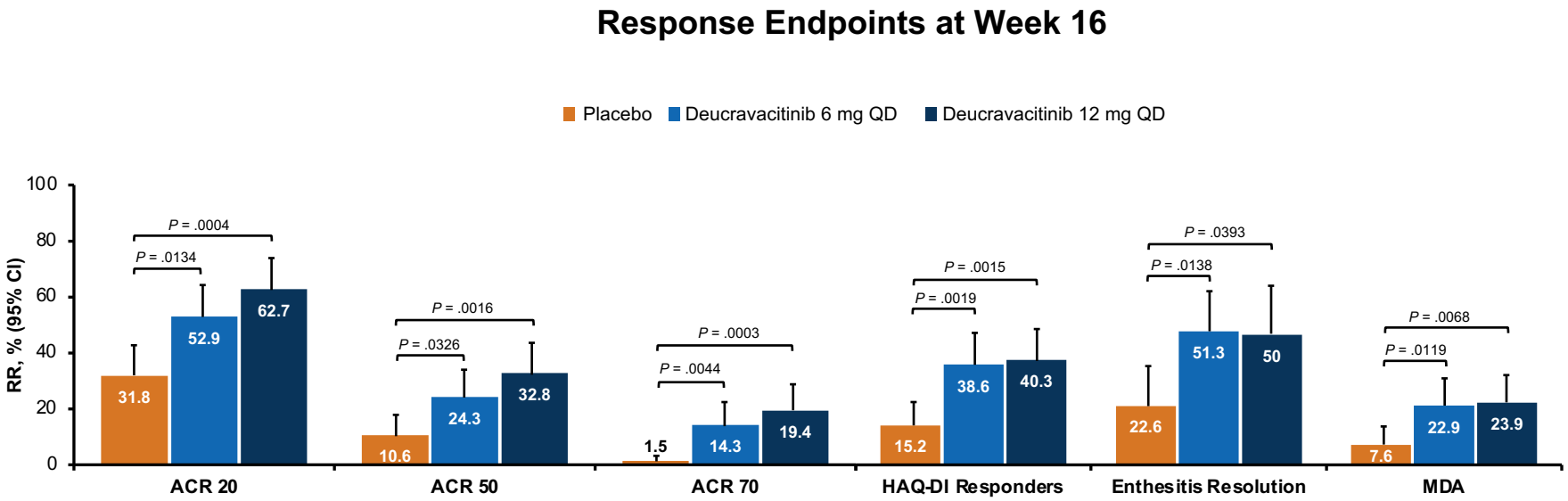
- No clinically significant trends were observed for laboratory parameters
- Similar results were observed between weeks 16-52

1. Armstrong A et al. 2021 AAD VMX.

Deucravacitinib Has Significant Potential to Be Broadly Applicable to a Range of Immune-Mediated Diseases

Indication	Relevant Pathways Inhibited via TYK2			Clinical Program Status/Expected Timing
Psoriasis	IL-12	IL-23		Filing pending
Psoriatic arthritis	IL-12	IL-23		Beginning Ph3
Ulcerative colitis	IL-12	IL-23		Ph2 POC 2021
Crohn's disease	IL-12	IL-23		Ph2 POC 2022
Lupus	IL-12	IL-23	Type 1 IFN	Ph2 POC 2022+

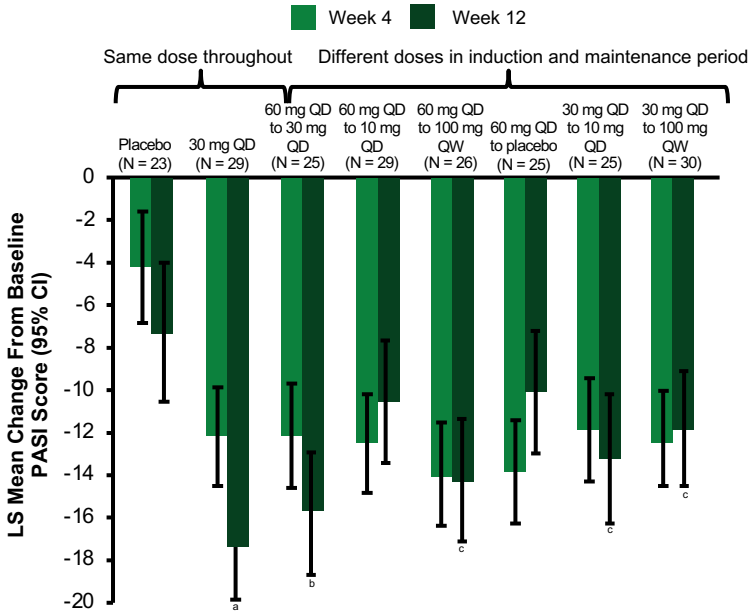
Deucravacitinib was Efficacious versus Placebo Over 16 Weeks in Patients with Active Psoriatic Arthritis[1]



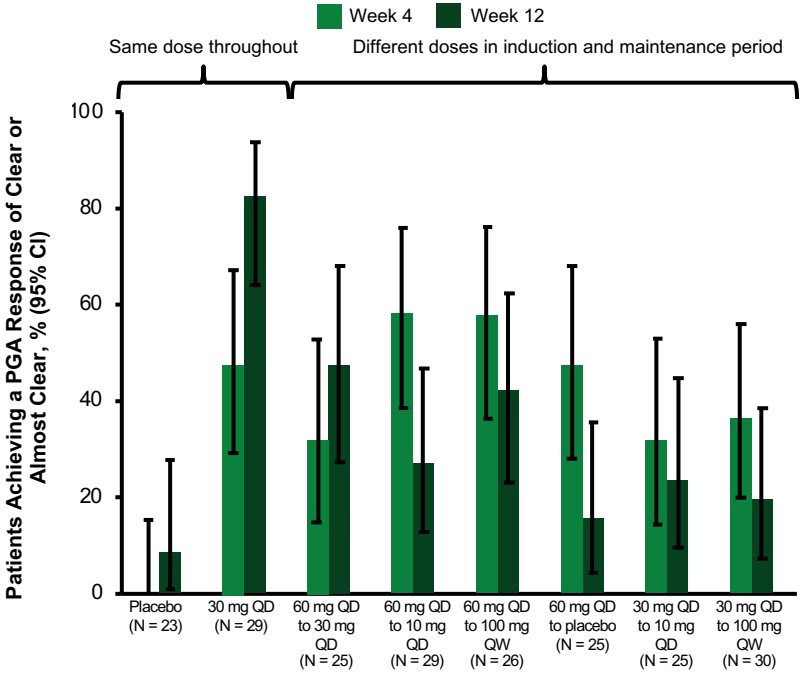
1. Mease P et al. *Ann Rheum Dis.* 2021;80:314-315.

Brepocitinib Generally Effective and Well Tolerated in Patients With Moderate to Severe Plaque Psoriasis: Phase 2a Trial[1]

Least Squares Mean Change From Baseline in PASI Score at Week 4 and Week 12 Across Dose Groups (MMRM)



Proportion of Patients Achieving PGA Response of Clear or Almost Clear at Week 4 and Week 12 Across Dose Groups (FAS, NRI)



[a] Hochberg $P < .0001$ versus placebo. [b] Hochberg $P < .001$ versus placebo. [c] Hochberg $P < .05$ versus placebo.

1. Forman SB et al. *J Invest Dermatol*. 2020;140:2359-2370.e5.

Brepocitinib: Current Status

A total of 149 patients developed AEs, with six serious AEs recorded in five patients[1]

- One patient died during the study (gunshot wound)
- No herpes zoster events occurred during this study

Development of oral brepocitinib for psoriasis has been discontinued; however, phase 2 trials are ongoing to evaluate the following

- Topical brepocitinib in mild to moderate psoriasis
- Oral brepocitinib in active PsA, moderate to severe ulcerative colitis (UC) and Crohn's disease (CD), hidradenitis suppurativa, and SLE

1. Forman SB et al. *J Invest Dermatol*. 2020;140:2359-2370.e5.

PF-06826647: Current Status

In a phase 1 randomized, double-blind, placebo-controlled, parallel-group study in patients with plaque psoriasis, PF-06826647 showed significant improvement in disease activity within 4 weeks of dosing with an acceptable safety profile[1]

A phase 2 trial in patients with moderate to severe plaque psoriasis was recently completed (NCT03895372); results have not been released yet

1. Tehlirian C et al. *Lancet Rheumatol.* 2020;3:E204-E213.

Additional Selective TYK2 Inhibitors in Clinical Development[1]

Agent	Company	Description	Status
GLPG3667	Galapagos	Active domain inhibitor	Ph1 in psoriasis
TYK2 Allosteric Inhibitor Research Program	Nimbus	Allosteric domain inhibitor	Ph1 in psoriasis
VTX-958	Ventyx Biosciences	Allosteric domain inhibitor	Ph1 in healthy volunteers
ESK-001	Esker Therapeutics	Allosteric domain inhibitor	Ph1 in healthy volunteers
BMS-986322	Bristol Myers Squibb	Unknown	Ph1 in healthy volunteers completed October 2020

1. https://www.evaluate.com/vantage/articles/interviews/esker-joins-tyk2-race.

Conclusions

- An improved understanding of psoriasis epidemiology, pathogenesis, and clinical burden has resulted in therapies that are efficacious for many patients
  - However, safety and efficacy concerns persist about some agents, preventing them from acquiring regulatory approval
- A substantial unmet need remains for safe and efficacious oral psoriasis therapies
  - This is currently being addressed via the development of oral, small-molecule, highly bioavailable kinase inhibitors, similar to the situation in other IMIDs (eg, JAK inhibitors in RA)

Conclusions (Cont'd)

- TYK2 regulates signaling and functional responses downstream of the IL-12, IL-23, and type 1 IFN receptors, each of which plays a central role in the pathophysiology of psoriasis
  - TYK2 has not previously been successfully targeted, but laboratory and clinical evidence suggests that allosteric inhibition of TYK2 might be a viable therapeutic approach

- Three TYK2 inhibitors are in development for moderate to severe psoriasis and PsA
  - Data from ongoing studies will clarify positioning and appropriate clinical use in the context of current treatment algorithms

Workshop

Expert Perspectives on Where Selective TYK2 Inhibition Fits Into the Expanding Psoriasis Treatment Armamentarium

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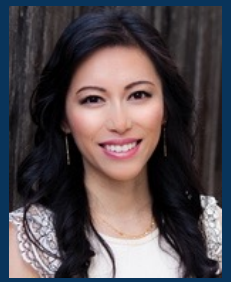

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Psoriasis: Unmet Needs Remain With Current Oral Options

~1.9 million patients
***Topicals*[a]**

Limited body surface use or adjunctive therapy for phototherapy and systemic therapies

~400,000 patients
***Current orals*[b]**

Apremilast PASI 75: 35% to 40%; tolerability concerns

~400,000 patients
Injectables

High PASI 75/90/100 rates; safety and burden considerations

- 2.7 million patients treated for moderate to severe psoriasis[c]
- Only ~30% treated with systemic therapy today
- High interest in oral therapy

[a] Includes patients treated with topicals and phototherapy only. [b] Includes apremilast, methotrexate, cyclosporine, and dimethyl fumarate (primarily in Germany).
[c] Numbers indicate patients on any prescribed treatment (topical, systemic, advanced) in G7 countries.
1. Decision Resources Group PsO Report.

Please remember to complete and submit your Post-Test and Evaluation for CME credit.

Missed anything?

PeerView.com/Psoriasis21

- Download the slides and Practice Aids by clicking the buttons located in the left-hand panel
- Watch the replay of this event
- Join the conversation on Twitter @PeerView

Thank you and good evening.

PeerView
Live

Abbreviations

- ADA: adalimumab
- APR: apremilast
- BID: twice daily
- BL: baseline
- CD4: cluster of differentiation 4
- CD8: cluster of differentiation 8
- DC: dendritic cell
- DEUC: deucravacitinib
- EPO: erythropoietin
- FAS: full analysis set
- G-CSF: granulocyte colony-stimulating factor
- GH: growth hormone
- GM-CSF: granulocyte–macrophage colony-stimulating factor
- GUS: guselkumab
- HAQ-DI: Health Assessment Questionnaire Disability Index
- IC_{50}: half maximal inhibitory concentration
- IL-1β: interleukin 1 beta
- IL-2: interleukin 2
- IL-4: interleukin 4
- IL-5: interleukin 5
- IL-6: interleukin 6
- IL-7: interleukin 7
- IL-9: interleukin 9
- IL-11: interleukin 11
- IL-12: interleukin 12
- IL-13: interleukin 13
- IL-15: interleukin 15
- IL-17: interleukin 17
- IL-19: interleukin 19
- IL-20: interleukin 20
- IL-21: interleukin 21
- IL-22: interleukin 22
- IL-23: interleukin 23
- IMID: immunomodulatory drug
- INF-α: interferon alpha
- INF-γ: interferon gamma

Abbreviations

- IXE: ixekizumab
- JAK: Janus kinase
- JAK1: Janus kinase 1
- JAK2: Janus kinase 2
- JAK3: Janus kinase 3
- LIF: leukemia inhibitory factor
- LS: least squares
- MACE: major adverse cardiovascular event
- MDA: minimal disease activity
- MMRM: mixed-effect model for repeated measures
- ND: no data
- NK: natural killer
- NMSC: nonmelanoma skin cancer
- NRI: nonresponse imputation
- OSM: oncostatin M
- PASI50: 50% reduction in the Psoriasis Area and Severity Index score
- PASI75: 75% reduction in the Psoriasis Area and Severity Index score
- PBO: placebo
- PDE4: phosphodiesterase-4
- PE: pulmonary embolism
- PGA: Physician's Global Assessment
- Ph2: phase 2
- Ph3: phase 3
- PsA: psoriatic arthritis
- PsO: psoriasis
- PSSD: Psoriasis Symptoms and Signs Diary
- QD: once daily
- RA: rheumatoid arthritis
- RIS: risankizumab
- RR: response rate
- SAE: serious adverse event
- SEC: secukinumab
- SF-36 PCS: Short Form-36 Physical Component Summary
- SLE: systemic lupus erythematosus
- sPGA: static Physician's Global Assessment

Abbreviations

- ss-PGA: scalp-specific Physician's Global Assessment
- STAT: signal transducer and activator of transcription
- STAT1: signal transducer and activator of transcription 1
- STAT2: signal transducer and activator of transcription 2
- STAT3: signal transducer and activator of transcription 3
- STAT4: signal transducer and activator of transcription 4
- T_H1: T helper type 1
- T_H17: T helper type 17
- T_H22: T helper type 22
- TNF: tumor necrosis factor
- TNF-α: tumor necrosis factor alpha
- TPO: thrombopoietin
- TYK2: tyrosine kinase 2
- TYK2i: tyrosine kinase 2 inhibitor
- UST: ustekinumab