TYK2: Pathological Drivers and Treatment Targets in Skin & Joint Conditions

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Disclosures

- **Consulting Fee:** AbbVie, Amgen, AstraZeneca, Bristol-Myers Squibb, Eli Lilly, GSK, Janssen, Novartis, Pfizer, Sanofi Genzyme, Schipher Medicine, UCB

- **Speakers Bureau:** AbbVie, Amgen, AstraZeneca, Bristol-Myers Squibb, Eli Lilly, Novartis, Sanofi Genzyme, UCB

Learning Objectives

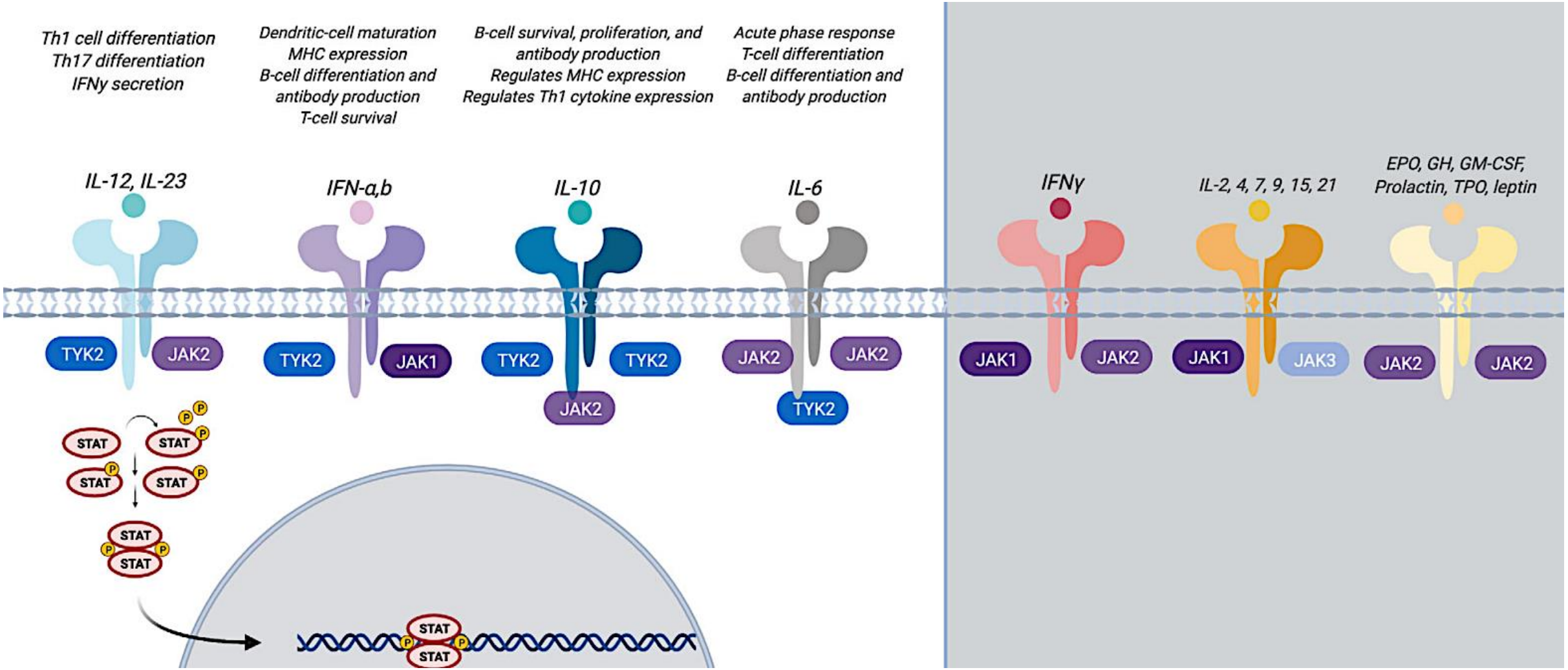
- **Review the mechanism of action of TYK2 signaling across rheumatic diseases**
- **Review clinical data of emerging therapies targeting the TYK2 pathway**

Tyrosine Kinase (TYK2) Signaling Pathways and Associated Treatment Targets

POLLING QUESTION

- **Which of the following cytokines is not regulated by TYK2?**
  - A. IL-6
  - B. IL-23
  - C. IFN-α
  - D. IFN-γ

JAK-Signal Transducers and Activators of STAT-Signaling Pathway

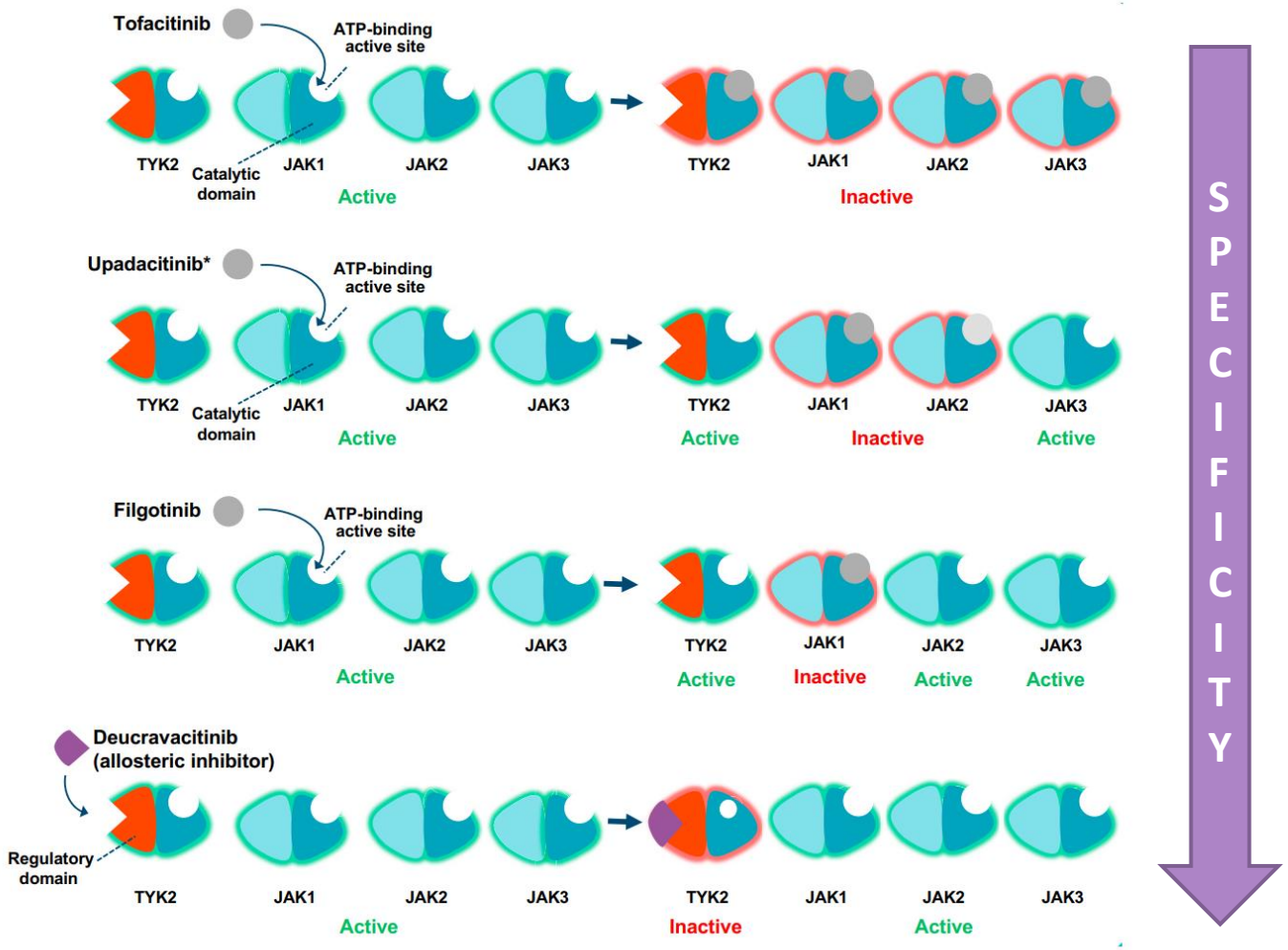


EPO= erythropoietin; GH = growth hormone; GM-CSF, granulocyte–macrophage colony-stimulating factor; IL, interleukin; IFN, interferon; TPO = thrombopoietin; TYK = tyrosine kinase

Schwartz D, et al. Nat Rev Drug Discov. 2017;16, 843-862

Evolution and Specificity of Therapies Inhibiting the JAK-STAT Pathway

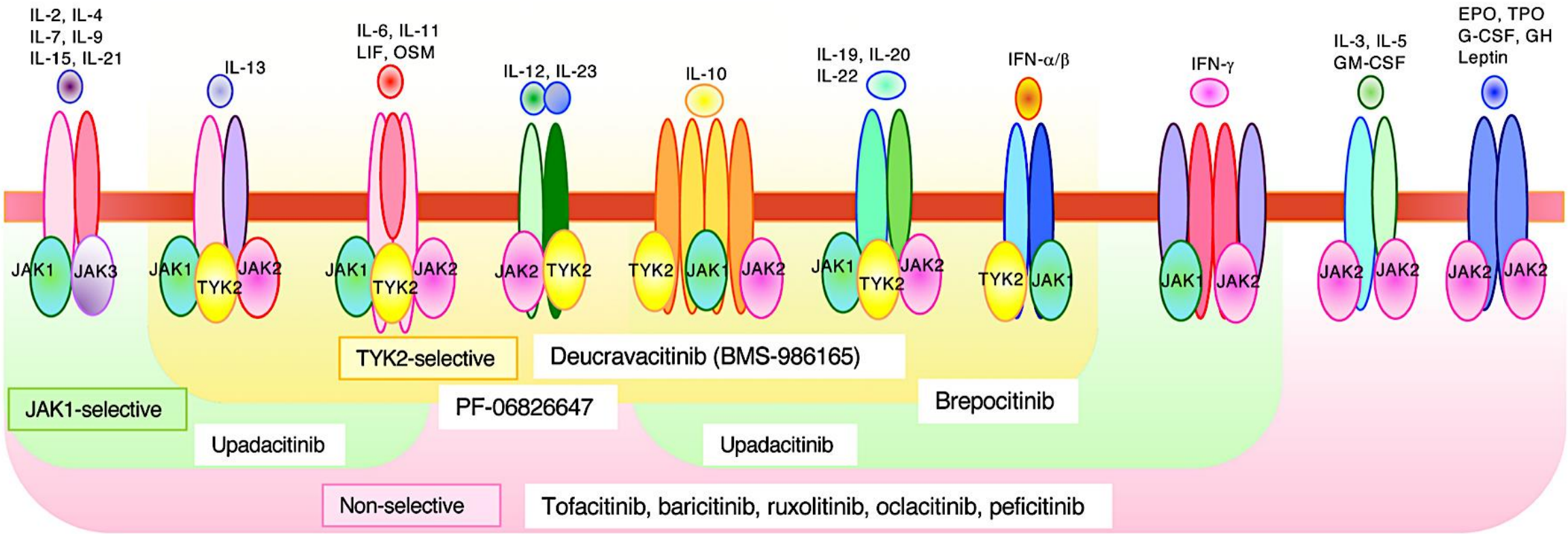
- **Pan-JAK**
  - Simultaneous inhibition suppresses multiple cytokine signaling that are essential for maintaining tissue homeostasis
  - Significant safety concerns
- **JAK 1-3**
  - More selective but not specific for the various JAK isoforms
  - Involved in critical functions such as hematopoiesis and immune response
  - Predictable AEs that were felt to be secondary to the broad inhibition of these functions
    - JAK2 inhibition → dose-dependent cytopenias due to reliance of EPO and TPO signaling
    - JAK3 inhibition → increased infections due to depletion of T, B, and NK cells
- **TYK2**
  - Involved in the pathogenesis of many immune-mediated diseases
  - Lack of serious adverse events (AEs) associated with the inhibition of other JAKs



EPO = erythropoietin; TPO = thrombopoietin

Jo CE, et al. Int J Dermatol. 2022 Feb;61(2):139-147; Nielsen OH, et al. Trends Pharmacol Sci. 2022 May;43(5):424-436; Krueger JG, et al. J Am Acad Dermatol. 2022 Jan;86(1):148-157.

Mechanism of Action of Emerging TYK2 Inhibitors

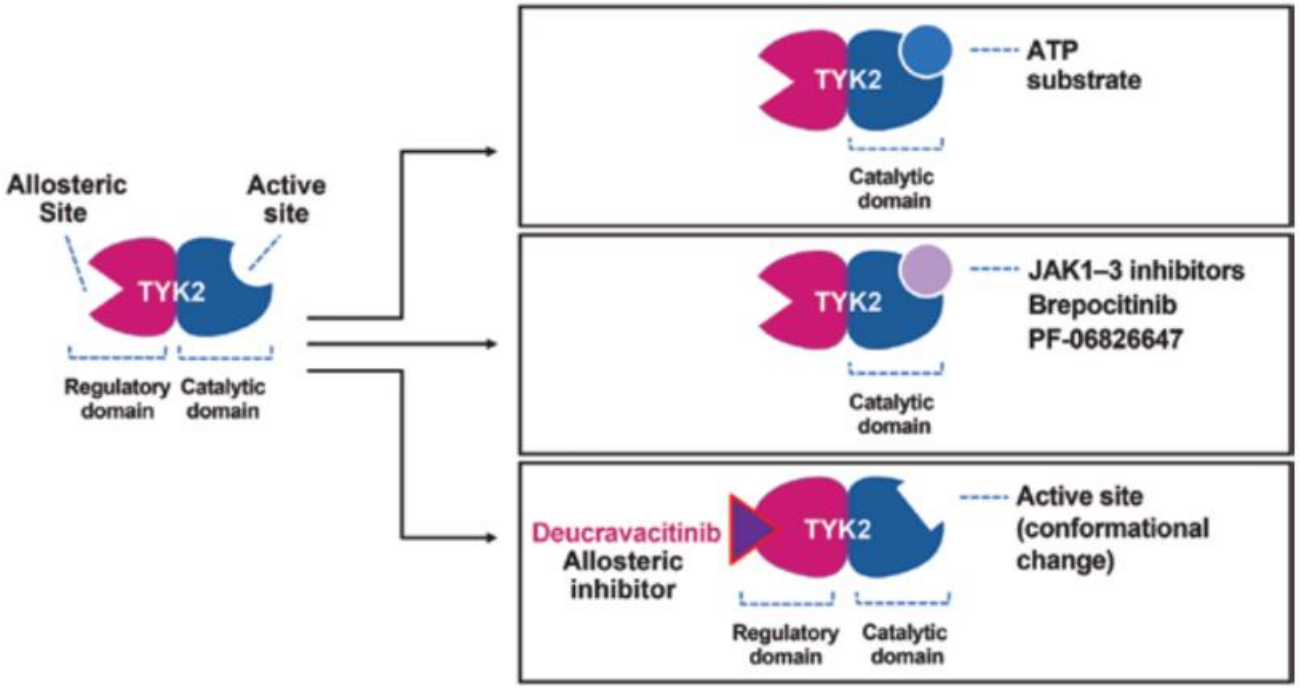


EPO = erythropoietin; G-CSF = granulocyte colony-stimulating factor; GH = growth hormone; GM-CSF = granulocyte–macrophage colony-stimulating factor; IL= interleukin; IFN=interferon; LIF=leukaemia inhibitory factor; OSM=oncostatin M; TPO= thrombopoietin; TYK= tyrosine kinase

Muromoto R, et al. World J Biol Chem 2022; 13(1): 1-14

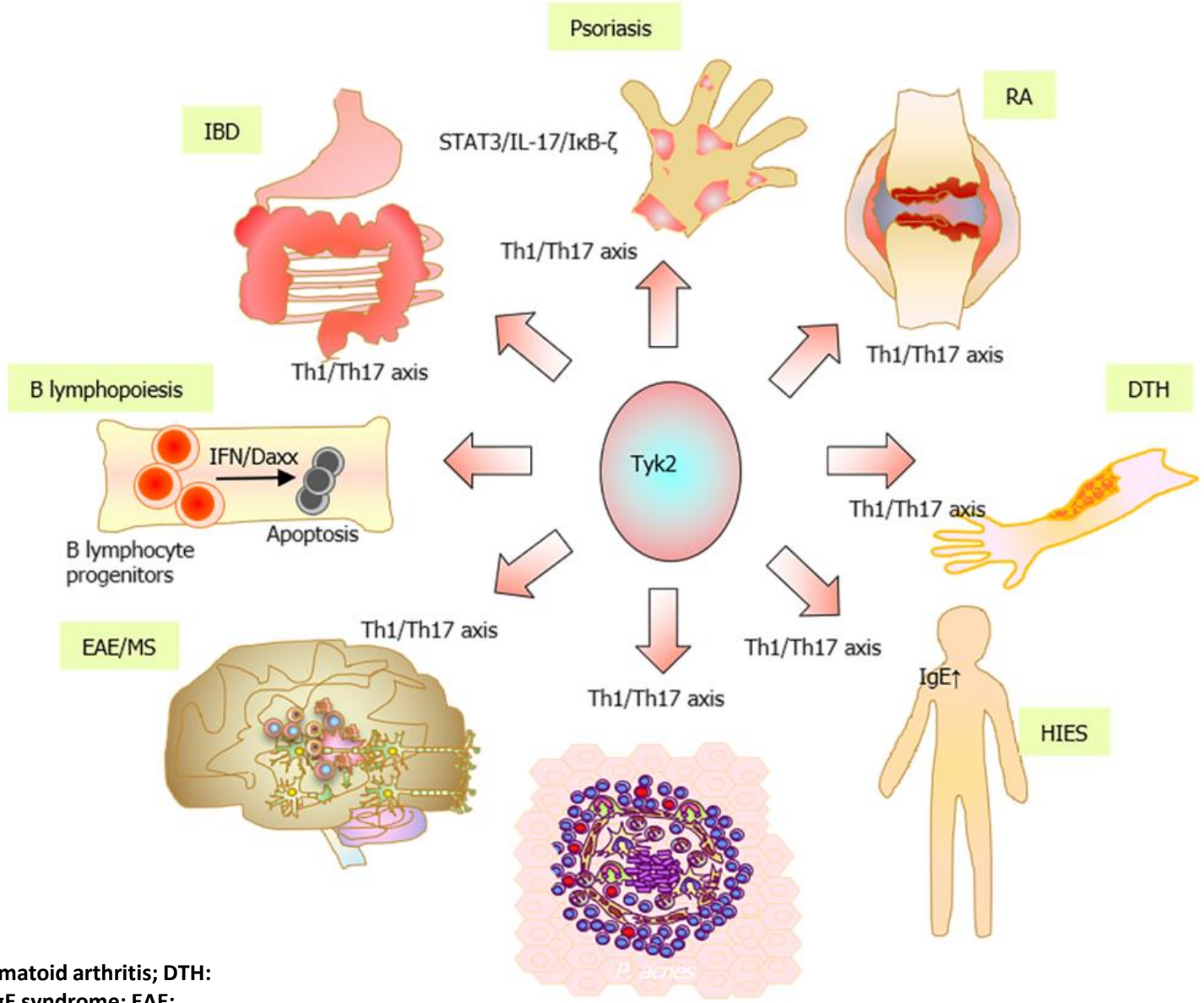
Selective vs Non-Selective TYK2 Inhibition

- **Deucravacitinib**
  - Inhibits TYK2 allosterically
  - Binds to the regulatory pseudokinase domain of TYK2
  - Locks the regulatory domain into an inhibitory interaction with the catalytic domain
- **Brepocitinib and PF-06826647**
  - Inhibit both TYK2 and JAK
  - Bind directly to the active site of the catalytic domain of TYK2



Burke JR, et al. Sci Transl Med. 2019;11:1-16; Wrobleski ST, et al. J Med Chem. 2019;62:8973-8995.

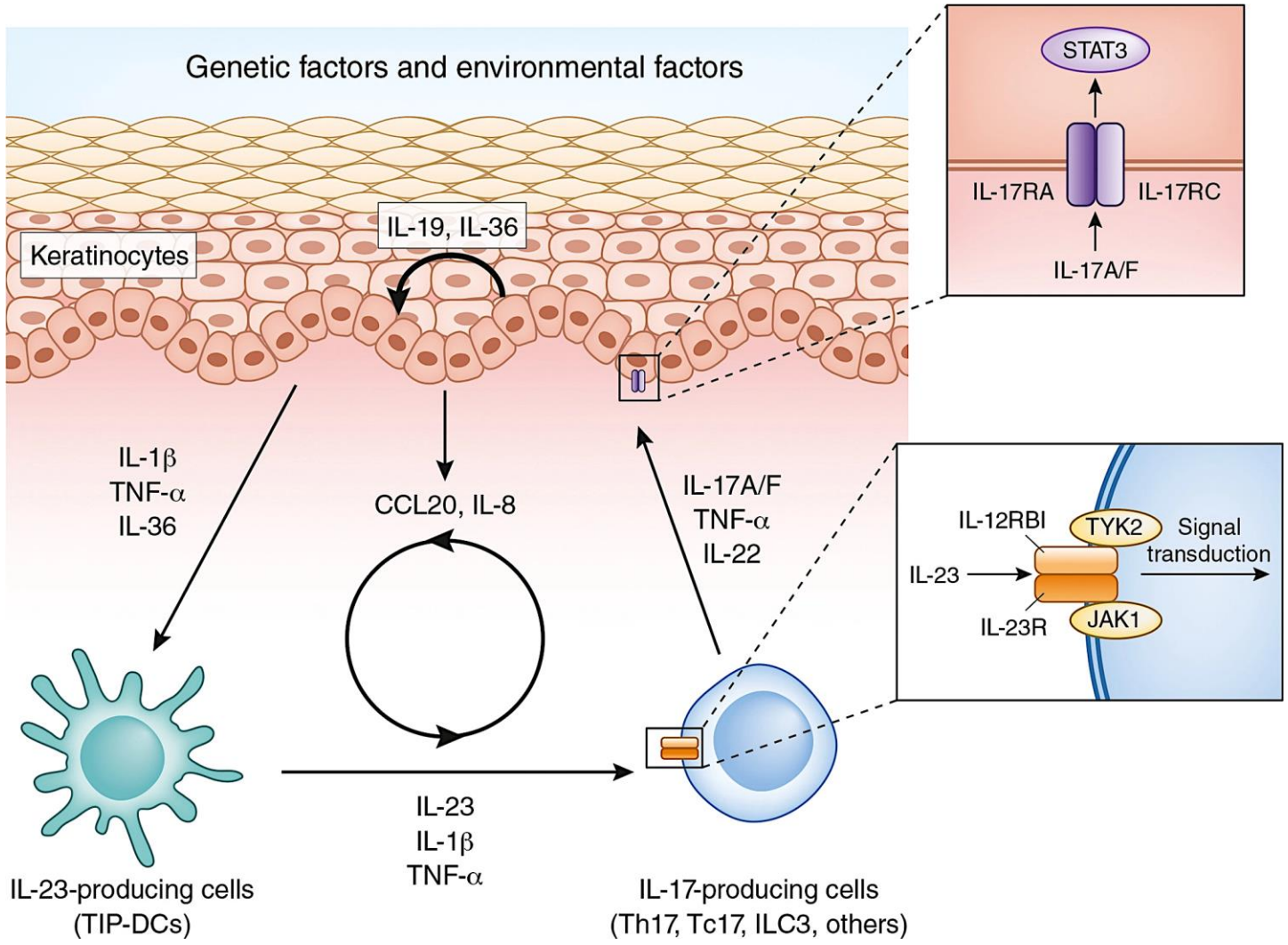
Potential Involvement of TYK2 in the Pathogenesis of Immune and Inflammatory Diseases



IBD: Inflammatory bowel diseases; RA: Rheumatoid arthritis; DTH: Delayed-type hypersensitivity; HIES: Hyper IgE syndrome; EAE: Experimental autoimmune encephalomyelitis; MS: Multiple sclerosis

Muromoto R, et al. World J Biol Chem 2022; 13(1): 1-14

Cytokine Involvement in Psoriasis



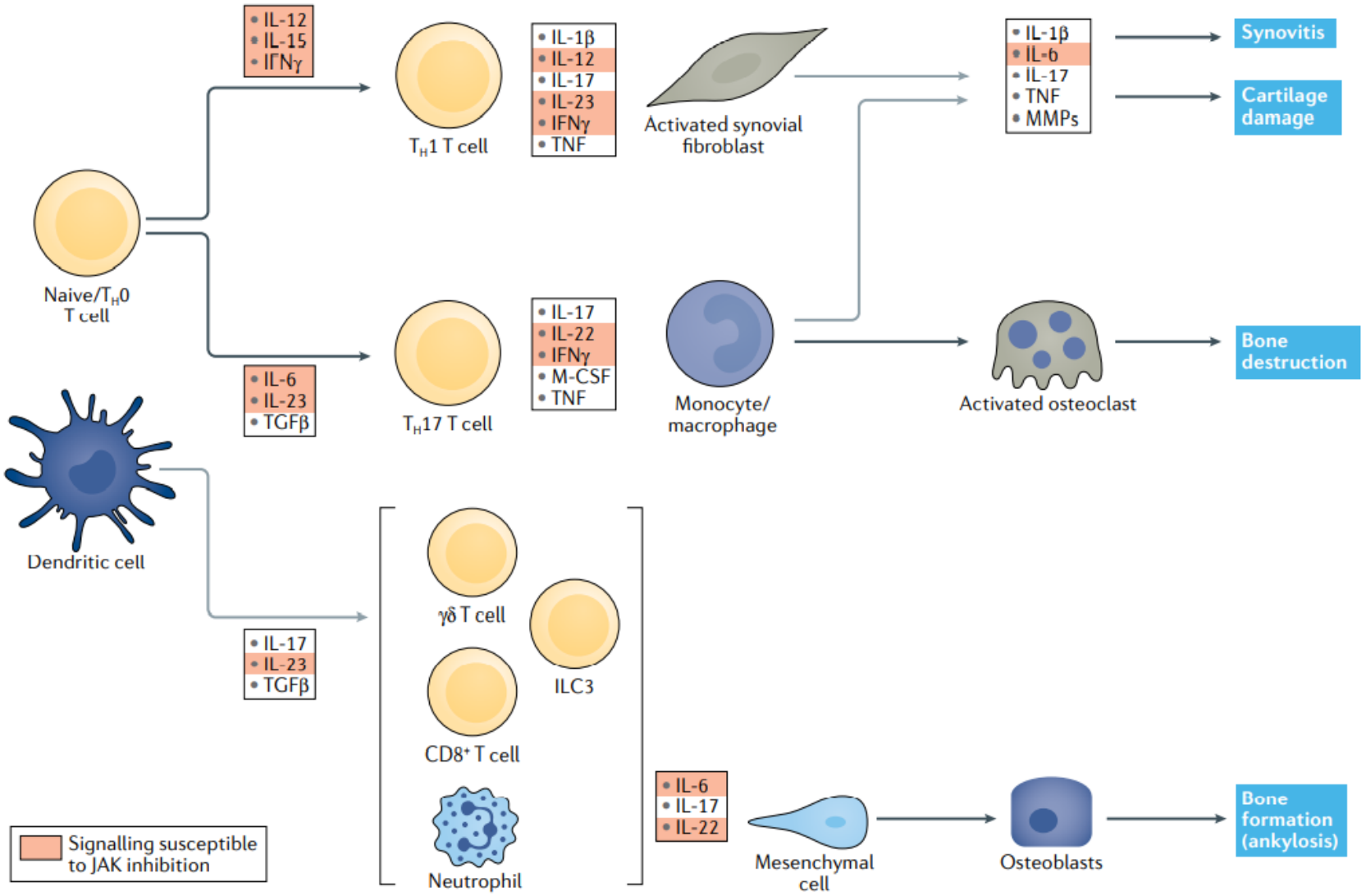
IL-23 initiates pathogenic Th17 cell activation and IL-17 production

IL-23 promotes survival and expansion of pathogenic Th17 cells

Persistent high levels of IL-23 sustain the production of IL-17, producing a feed-forward inflammatory reaction

Yamanaka K, et al. J Dermatol. 2021 Jun;48(6):722-731.

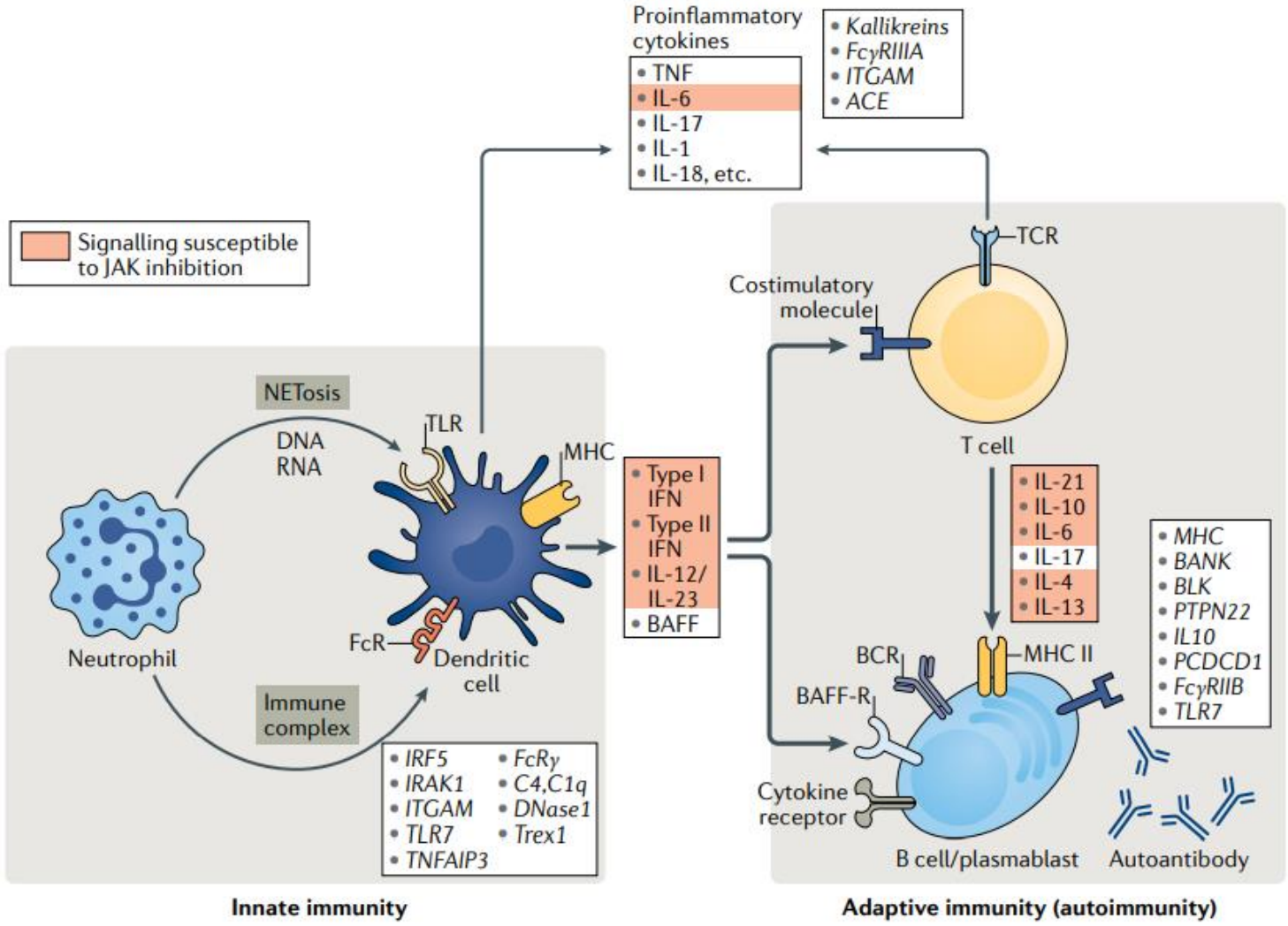
Cytokine Involvement in Spondyloarthritis



ILC3=type 3 innate lymphoid cells; M-CSF=macrophage colony-stimulating factor; MMPs = matrix metalloproteinases; TGFβ = transforming growth factor-β.

Tanaka Y, et al. Nat Rev Rheumatol. 2022 Mar;18(3):133-145.

Cytokine Involvement in Systemic Lupus Erythematosus



BAFF-R, BAFF receptor; BCR, B cell receptor; FcR, Fc receptor; MHC, major histocompatibility complex; NET, neutrophil extracellular trap; TCR, T cell receptor.

Tanaka Y, et al. Nat Rev Rheumatol. 2022 Mar;18(3):133-145.

Emerging TYK2 Inhibitors in Late-Stage Clinical Trials

Agent	Target / Selectivity	Clinical Trials
Deucravacitinib (BMS-986165)	TYK2	Psoriasis – Phase 3 Psoriatic arthritis – Phase 2 SLE – Phase 2
Brepocitinib (PF-06700841)	JAK1 / TKY2	Psoriasis – Phase 2 Psoriatic arthritis – Phase 2 Alopecia areata – phase 2 Vitiligo – Phase 2 SLE – Phase 2 AD – Phase 2 HS – Phase 2
Ropsacitinib (PF-06826647)	TYK2	Psoriasis – Phase 2 HS – Phase 2

AD = atopic dermaittits; SLE = Systemic Lupus Erythematosus; HS = Hidradenitis suppurativa

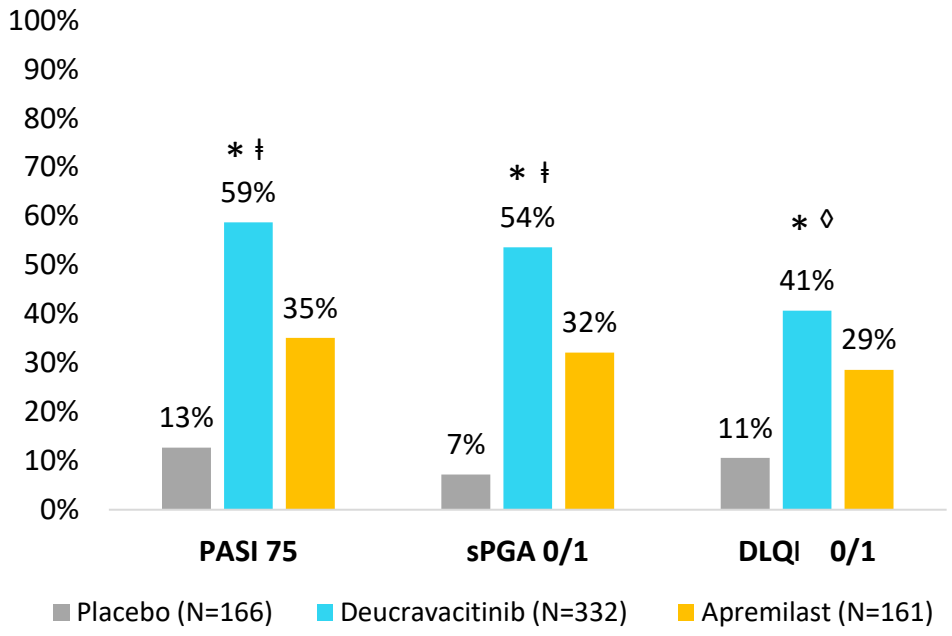
FDA. Drug Approvals and Databases. Available at: https://www.fda.gov/drugs/development-approval-process-drugs/drug-approvals-and-databases. Accessed 7/14/22; Clinical Trials. Available at https://clinicaltrials.gov. Accessed /14/22.

Key Data from Clinical Trials: Deucravacitinib

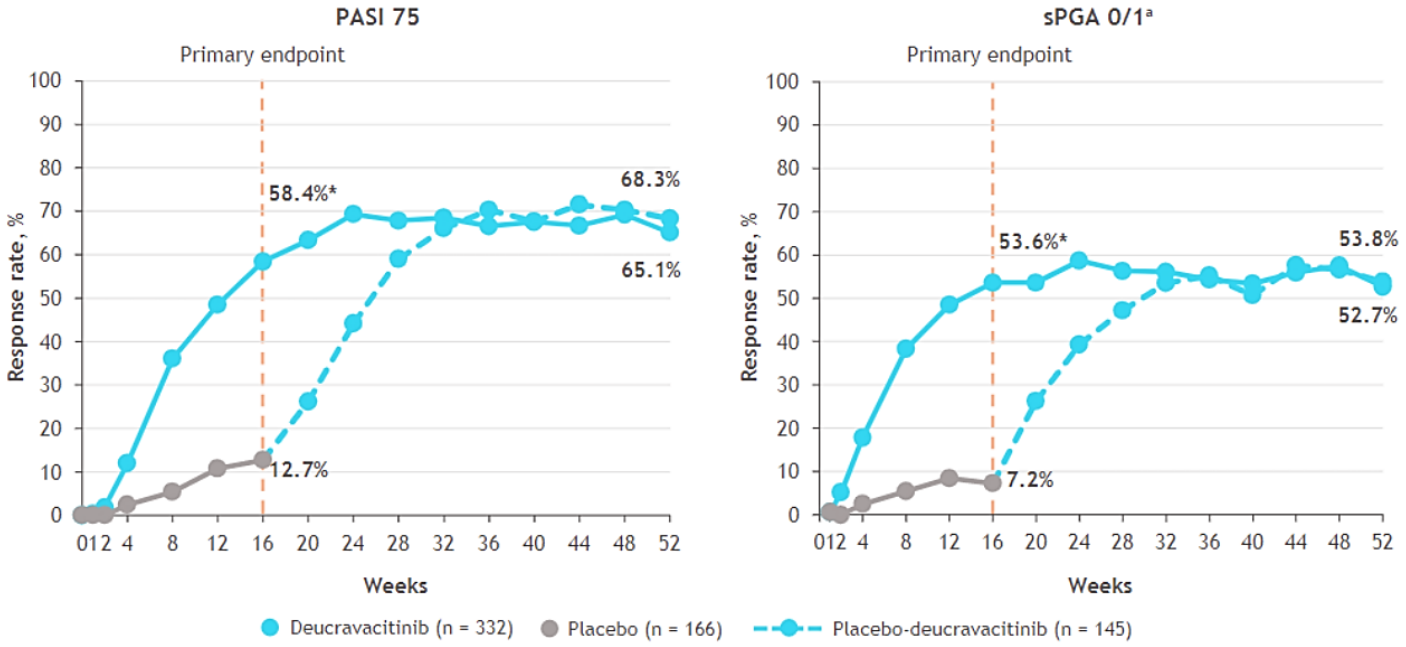
Deucravacitinib: Efficacy in Moderate to Severe Psoriasis

POETYK PSO-1 and -2 Phase 3 clinical trials to evaluate deucravacitinib (6mg QD) vs apremilast (30mg BID) and vs placebo in patients with moderate to severe PsO through 52 weeks of treatment

Outcomes at Week 16



Outcomes Through Week 52



*p<0.0001 vs placebo; ǂp<0.0001 vs apremilast ;◊p=0.01 vs apremilast

SPGA = static Physician's Global Assessment; DLQI = Dermatology Life Quality Index

Armstrong A, et al. Ann Rheum Dis. 2021;80(Suppl 1):795-796;
Warren RB, et al. SKIN The Journal of Cutaneous Medicine, 6(2), s4;

Deucravacitinib: Long Term Efficacy in PsO

2-Year Results From the Phase 3 POETYK PSO Program

Type of sensitivity analysis	Deucravacitinib — Deucravacitinib				Placebo — Deucravacitinib				Apremilast — Deucravacitinib				Total			
	Week 0		Week 60		Week 0		Week 60		Week 0		Week 60		Week 0		Week 60	
	n	Mean response rate (%)	n	Mean response rate (%)	n	Mean response rate (%)	n	Mean response rate (%)	n	Mean response rate (%)	n	Mean response rate (%)	n	Mean response rate (%)	n	Mean response rate (%)
PASI 75																
TFR	944	70.8	705	77.7	197	34.5	127	87.4	80	73.8	70	87.1	1221	65.1	902	79.8
Modified NRI	805	71.3	805	75.7	138	37.0	138	87.4	79	74.7	79	84.8	1022	66.9	1022	78.1
As-observed analysis	944	70.8	690	79.4	197	34.5	124	89.5	80	73.8	70	87.1	1221	65.1	884	81.4
PASI 90																
TFR	944	43.6	705	49.6	197	15.7	127	53.5	80	40.0	70	62.9	1221	38.9	902	51.2
Modified NRI	805	44.5	805	47.3	138	17.4	138	54.2	79	40.5	79	60.1	1022	40.5	1022	49.3
As-observed analysis	944	43.6	690	50.7	197	15.7	124	54.8	80	40.0	70	62.9	1221	38.9	884	52.3
sPGA 0/1																
TFR	944	56.0	705	58.7	197	25.4	126	65.1	80	53.8	70	72.9	1221	50.9	901	60.7
Modified NRI	805	56.3	805	57.1	138	27.5	138	65.0	79	54.4	79	70.7	1022	52.3	1022	59.2
As-observed analysis	944	56.0	690	60.0	197	25.4	123	66.7	80	53.8	70	72.9	1221	50.9	883	61.9

TFR = Treatment failure rules; NRI was implemented for patients who discontinued treatment due to worsening of PsO or lack of efficiency. Modified NRI = multiple imputation was used for patients with missing data, and patients who discontinued due to worsening of PsO only were imputed as non-responders (includes patients who reached week 60 or discontinued by Oct 1, 2021).

Warren RB, et al. POS1046. Presented at EULAR 2022. June 1-4 2022. Copenhagen & Virtual

Deucravacitinib: Long Term Safety in PsO

Overall Safety Summary at 1- vs 2-years

AE category	At 1 year[a] (PSO-1 + PSO-2) Deucravacitinib 6 mg QD (N = 1364) Total PY = 969.0		At 2 years[b] (PSO-1 + PSO-2 + LTE) Deucravacitinib 6 mg QD (N = 1519) Total PY = 2482.0	
	n (%)	EAIR/100 PY	n (%)	EAIR/100 PY
AEs	995 (72.9)	229.2	1214 (79.9)	154.4
SAEs	55 (4.0)	5.7	145 (9.5)	6.1
Discontinued treatment due to AEs	43 (3.2)	4.4	69 (4.5)	2.8
Deaths	2 (0.1)	0.2	10 (0.7)	0.4
Most common AEs (≥ 5% of patients)	**n (%)**	**EAIR/100 PY**	**n (%)**	**EAIR/100 PY**
Nasopharyngitis	229 (16.8)	26.1	271 (17.8)	12.9
Upper respiratory tract infection	124 (9.1)	13.4	150 (9.9)	6.5
COVID-19	5 (0.4)	0.5	124 (8.2)	5.1
Headache	80 (5.9)	8.5	99 (6.5)	4.2
Arthralgia	55 (4.0)	5.7	85 (5.6)	3.5
Diarrhea	69 (5.1)	7.3	84 (5.5)	3.5

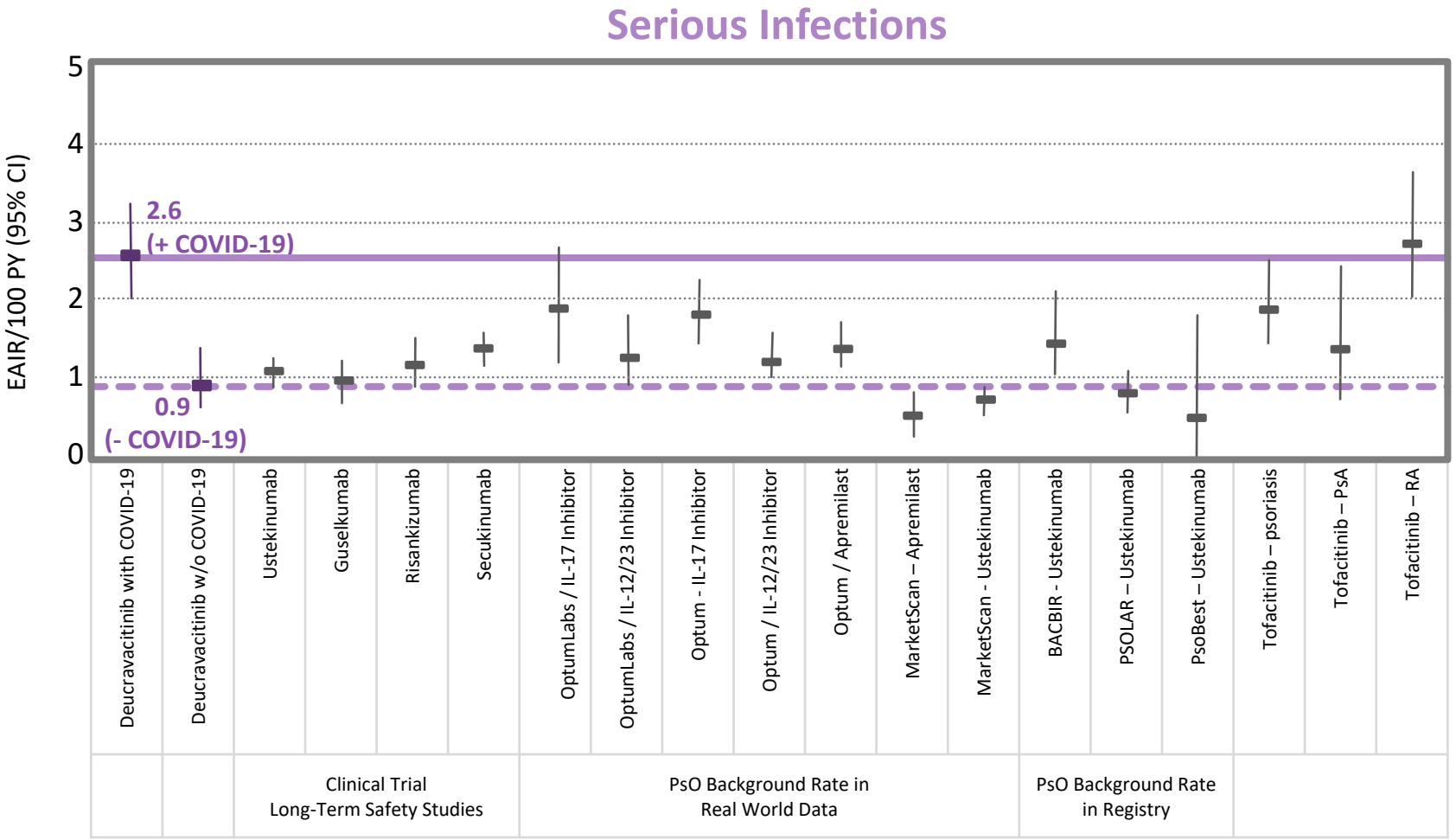
AEs of Interest at 1- vs 2-years

AE category	At 1 year[a] (PSO-1 + PSO-2) Deucravacitinib 6 mg QD (N = 1364) Total PY = 969.0		At 2 years[b] (PSO-1 + PSO-2 + LTE) Deucravacitinib 6 mg QD (N = 1519) Total PY = 2482.0	
	n (%)	EAIR/100 PY	n (%)	EAIR/100 PY
Serious infections	17 (1.2)	1.7	64 (4.2)	2.6
Herpes zoster infection	8 (0.6)	0.8	17 (1.1)	0.7
Total COVID-19 infection	5 (0.4)	0.5	124 (8.2)	5.1
Serious COVID-19 infection	2 (0.1)	0.2	30 (2.0)	1.2
COVID-19 pneumonia	0 (0)	0.0	13 (0.9)	0.5
COVID-19-related deaths	0 (0)	0.0	6 (0.4)	0.2
MACE[c]	3 (0.2)	0.3	9 (0.6)	0.4
VTE[d]	2 (0.1)	0.2	3 (0.2)	0.1
Total malignancies	10 (0.7)	1.0	22 (1.4)	0.9
NMSC	7 (0.5)	0.7	11 (0.7)	0.4
Malignancies excluding NMSC	3 (0.2)	0.3	12 (0.8)	0.5
Lymphoma	1 (0.1)	0.1	3 (0.2)	0.1

AE = adverse events; EAIR = exposure-adjusted incidence rate; LTE = long-term extension; MACE = major adverse cardiovascular event; NMSC = non-melanoma skin cancer; PY = patient years; SAEs = serious adverse events; VTE = Venous thromboembolism.

Warren RB, et al. POS1046. Presented at EULAR 2022. June 1-4 2022. Copenhagen & Virtual

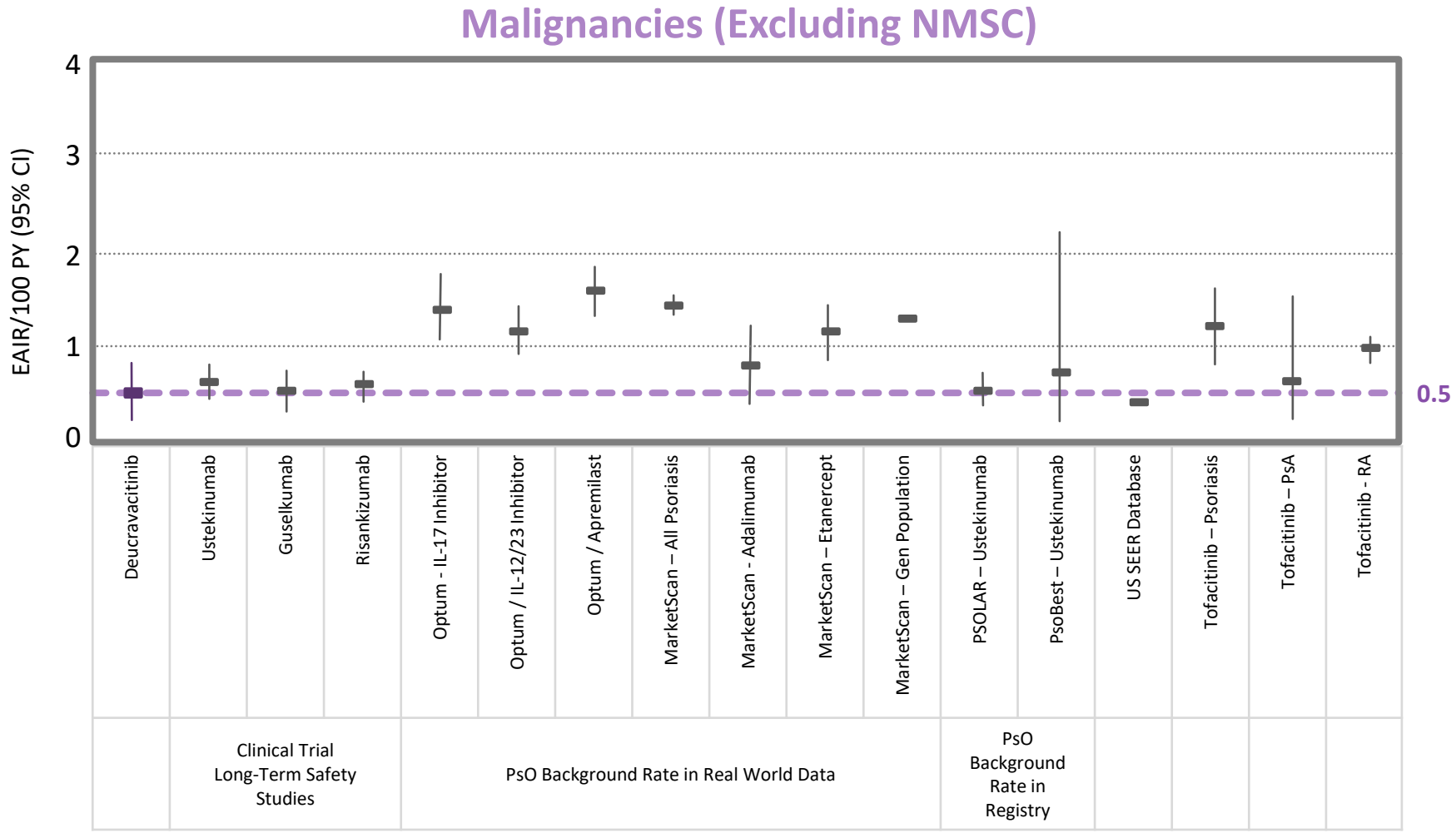
Deucravacitinib: EAIR for Infections at 2-years vs Other PsO Therapies*



EAIR = exposure-adjusted incidence rate
***Long-term safety data, real-world studies, or registry studies of other systemic psoriasis therapies.**

Warren RB, et al. POS1046. Presented at EULAR 2022. June 1-4 2022. Copenhagen & Virtual

Deucravacitinib: EAIR for Malignancies at 2-years vs Other PsO Therapies*

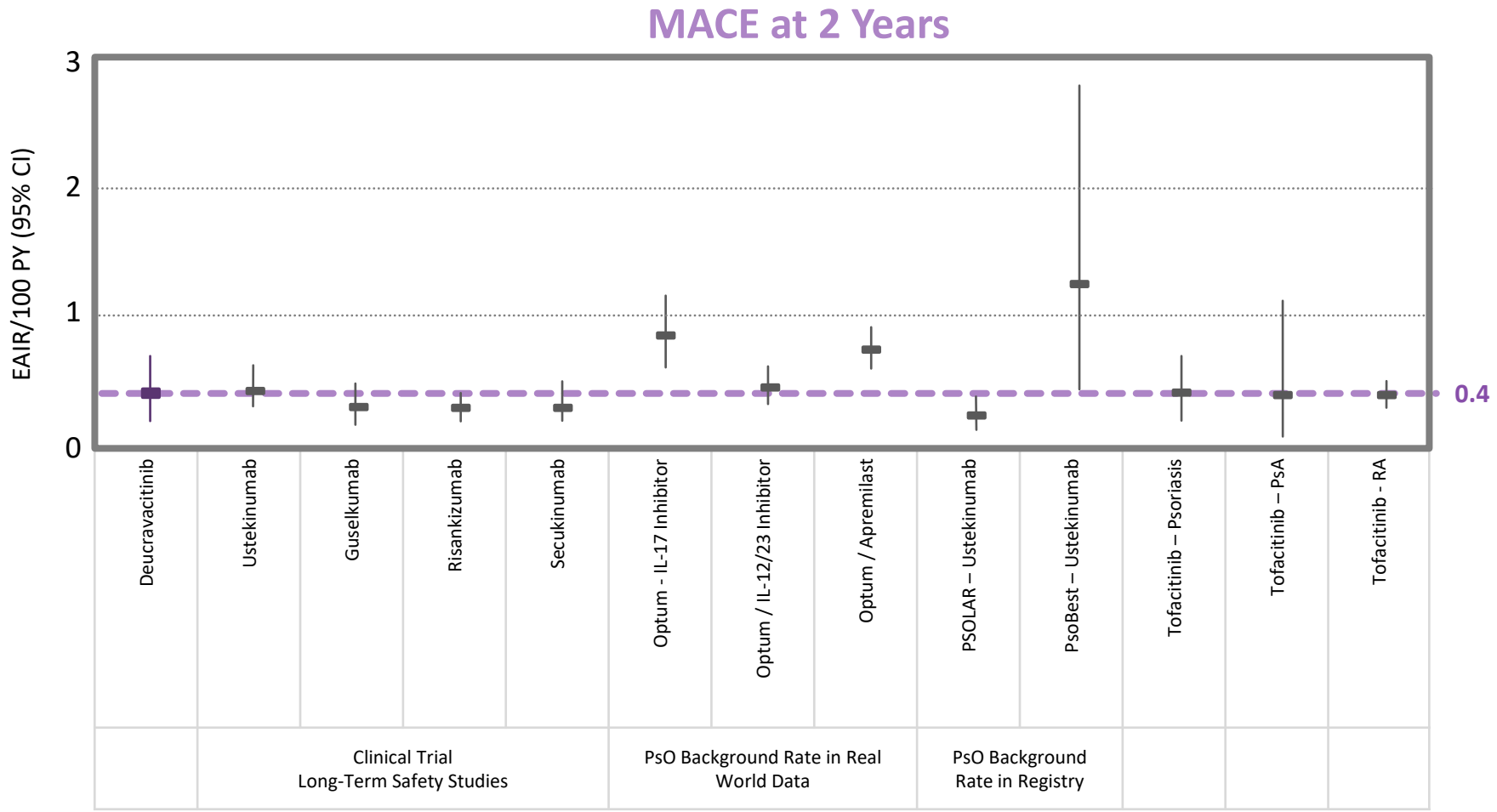


NMSC=nonmelanoma skin cancer.

***Long-term safety data, real-world studies, or registry studies of other systemic psoriasis therapies.**

Warren RB, et al. POS1046. Presented at EULAR 2022. June 1-4 2022. Copenhagen & Virtual

Deucravacitinib: EAIR for MACE at 2-years vs Other PsO Therapies*



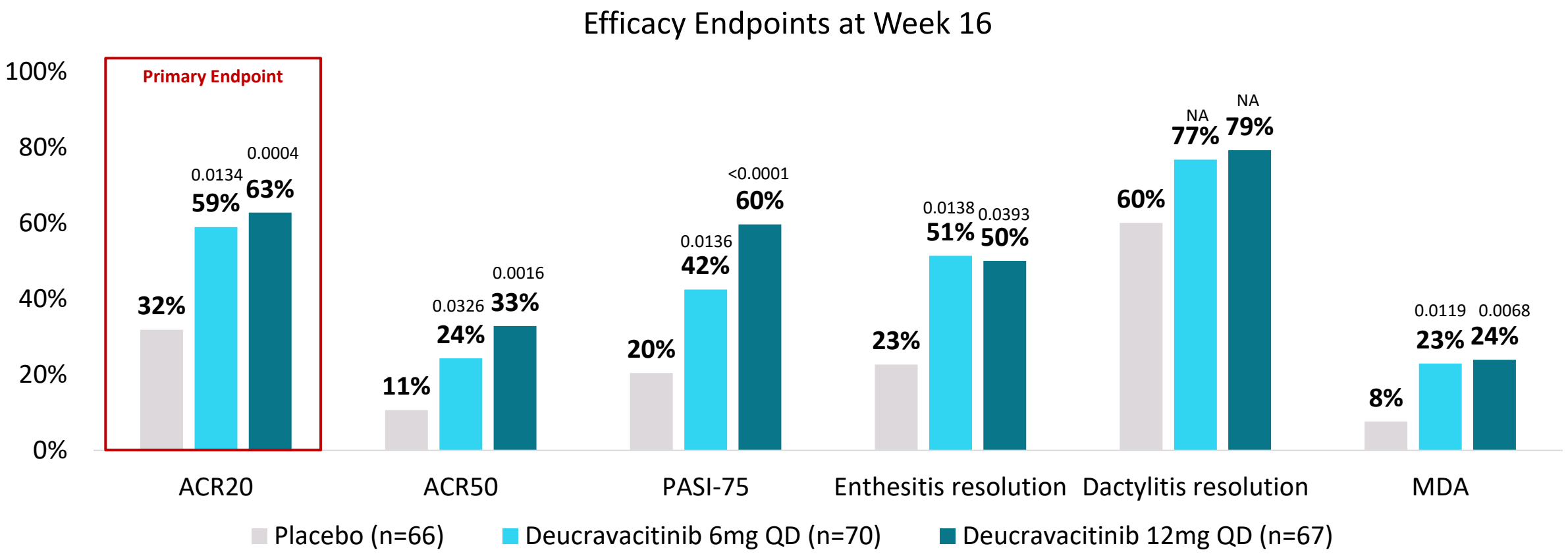
MACE =major adverse cardiovascular event.

***Long-term safety data, real-world studies, or registry studies of other systemic psoriasis therapies.**

Warren RB, et al. POS1046. Presented at EULAR 2022. June 1-4 2022. Copenhagen & Virtual

Deucravacitinib: Effectiveness in Active Psoriatic Arthritis

Phase 2 clinical trial to evaluate deucravacitinib (6mg QD and 12mg QD) vs placebo in active PsA for 16-weeks



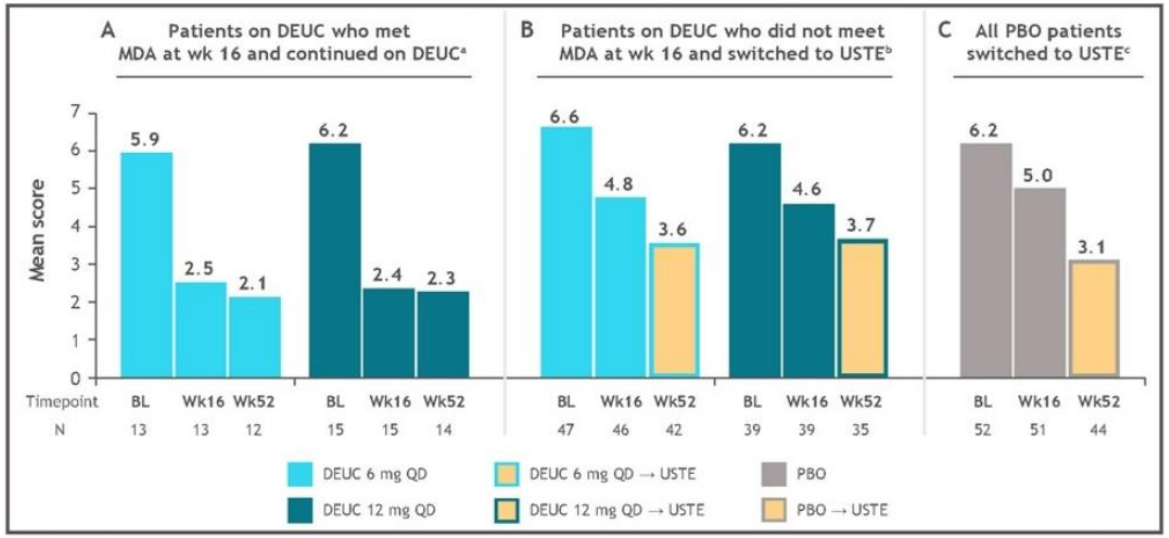
MDA = minimal disease activity.

Mease PJ, et al. Ann Rheum Dis. 2022 Jun;81(6):815-822.

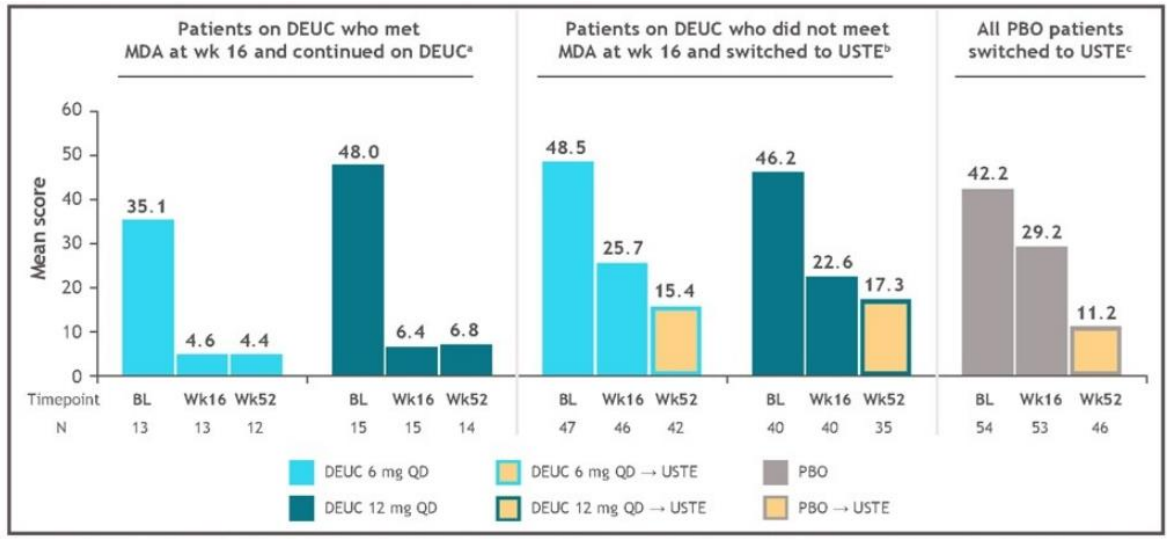
Deucravacitinib: 1-Year Comparative Effectiveness in PsA

Extension of Phase 2 clinical trial with re-randomization of patients to deucravacitinib (6mg QD and 12mg QD) or ustekinumab based on response

Mean PASDAS Scores



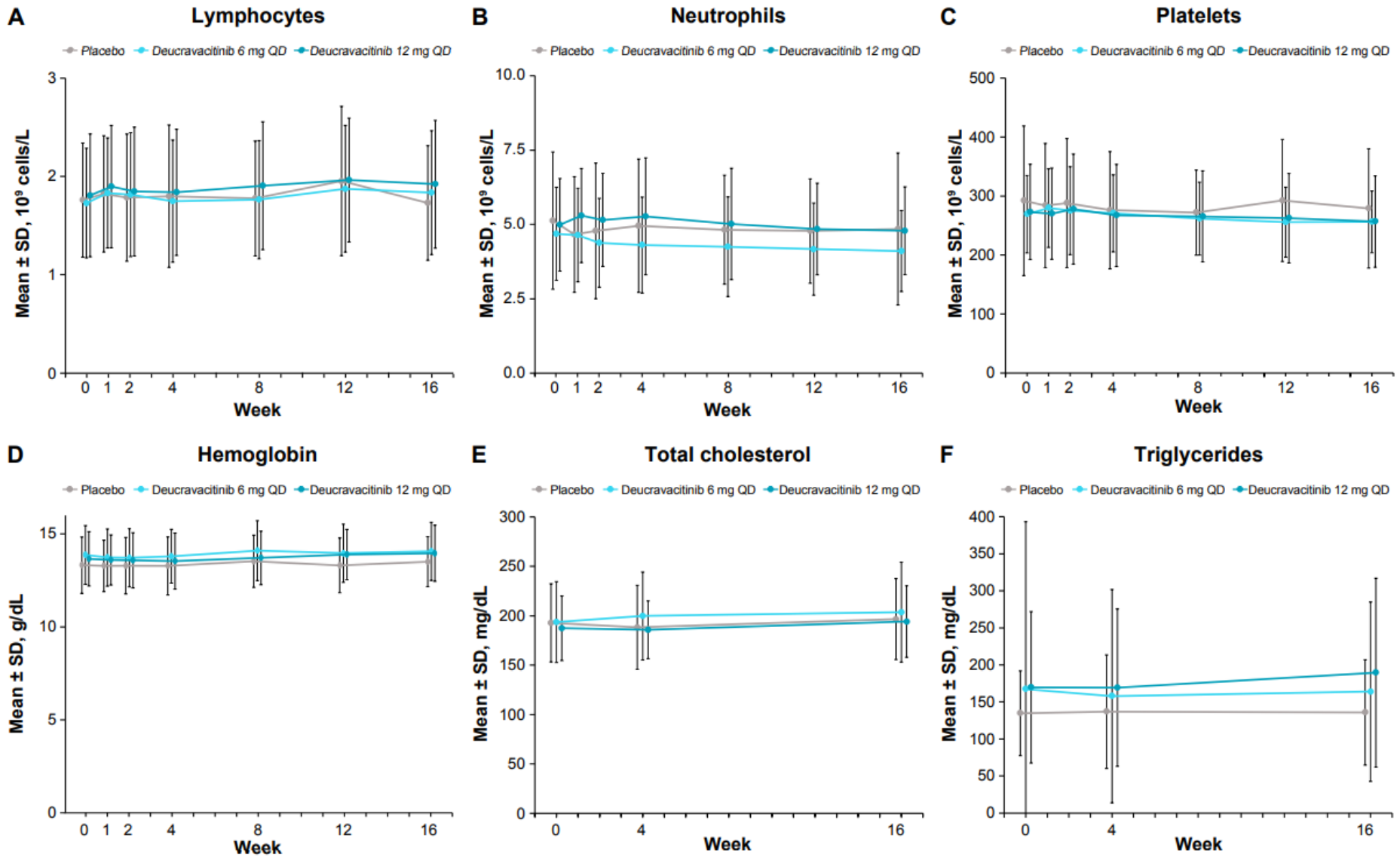
Mean DAPSA Scores



BL = baseline; DAPSA = Disease Activity in PSoriatic Arthritis; DEUC = deucravacitinib; MDA= minimal disease activity; PASDAS = Psoriatic Arthritis Disease Activity Scores; PBO = placebo; UTSE = ustekinumab.

Mease PJ, et al. POS1048. Presented at EULAR 2022. June 1-4 2022. Copenhagen & Virtual

Deucravacitinib: Laboratory Parameters in PsA

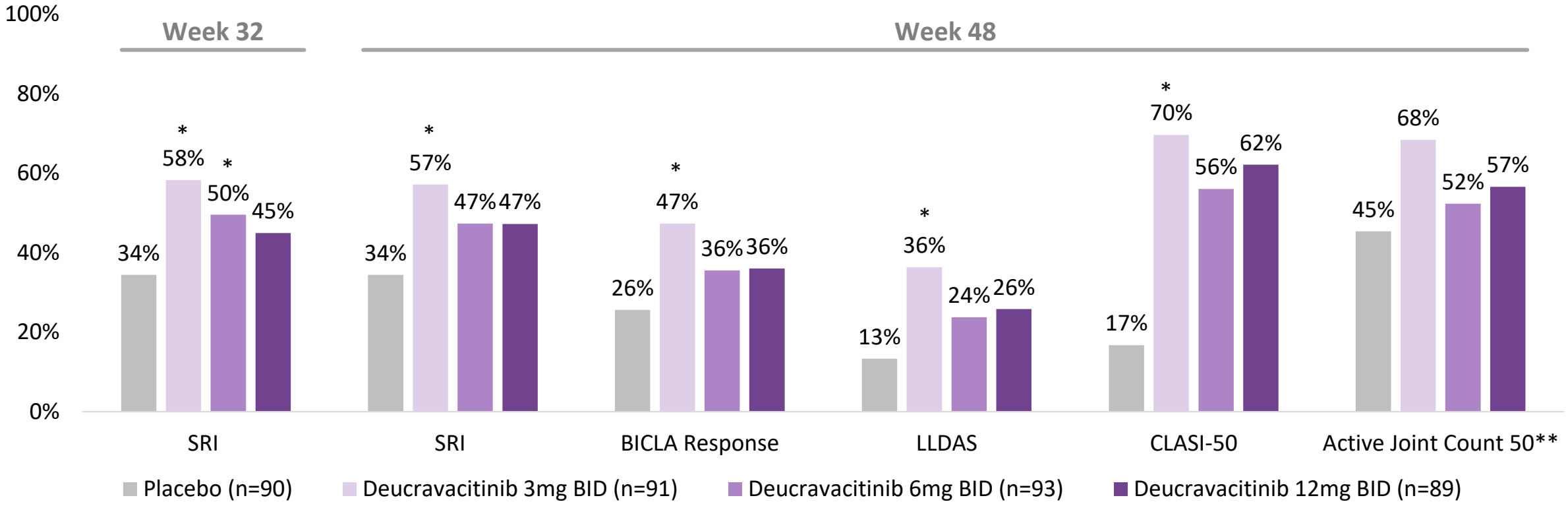


Mease PJ, et al. Ann Rheum Dis. 2022 Jun;81(6):815-822.

Deucravacitinib: Effectiveness in Active Systemic Lupus Erythematosus

Phase 2 clinical trial to evaluate deucravacitinib (3 mg BID, 6 mg BID, 12 mg QD) vs placebo in patients with active SLE for 48-weeks

Key Efficacy Outcomes



*** P value was significant vs placebo; **Exploratory endpoint (defined as patients with ≥6 tender/swollen joints at baseline, who have ≥50% decrease from BL in active joints.**

BICLA =British Isles Lupus Assessment Group–based Composite Lupus Assessment; CLASI = Cutaneous Lupus Erythematosus Disease Area and Severity Index; LLDAS =Lupus Low Disease Activity State ; SRI = SLE Responder Index.

Morand E, et al. Annals of the Rheumatic Diseases 2022;81:209.

Deucravacitinib: Safety in SLE

Safety Events Through Week 48

AE, n[a] (%)	Placebo n = 90	DEUC 3 mg BID n = 91	DEUC 6 mg BID n = 93	DEUC 12 mg QD n = 89
AE	79 (87.8)	85 (93.4)	81 (87.1)	75 (84.3)
SAE	11 (12.2)	7 (7.7)	8 (8.6)	7 (7.9)
AEs leading to treatment discontinuation	3 (3.3)	8 (8.8)	6 (6.5)	11 (12.4)
Skin-related AEs[b]	12 (13.3)	15 (16.5)	32 (34.4)	30 (33.7)
Overall infections/ infestations	48 (53.3)	60 (65.9)	60 (64.5)	45 (50.6)
Serious infections/ infestations	1 (1.1)	1 (1.1)	2 (2.2)	1 (1.1)
Infections of interest				
Tuberculosis	0	0	0	0
Herpes zoster[c]	4 (4.4)	3 (3.3)	3 (3.2)	2 (2.2)
Influenza	1 (1.1)	3 (3.3)	1 (1.1)	3 (3.4)
COVID-19	3 (3.3)	3 (3.3)	5 (5.4)	3 (3.4)
Malignancy events	1 (1.1)[d]	1 (1.1)[e]	0	1 (1.1)[f]
MACE	0	0	0	0
Thrombotic events	0	0	0	0

AE = adverse event; DEUC = deucravacitinib; MACE = major adverse cardiovascular event; SAE = serious adverse event.

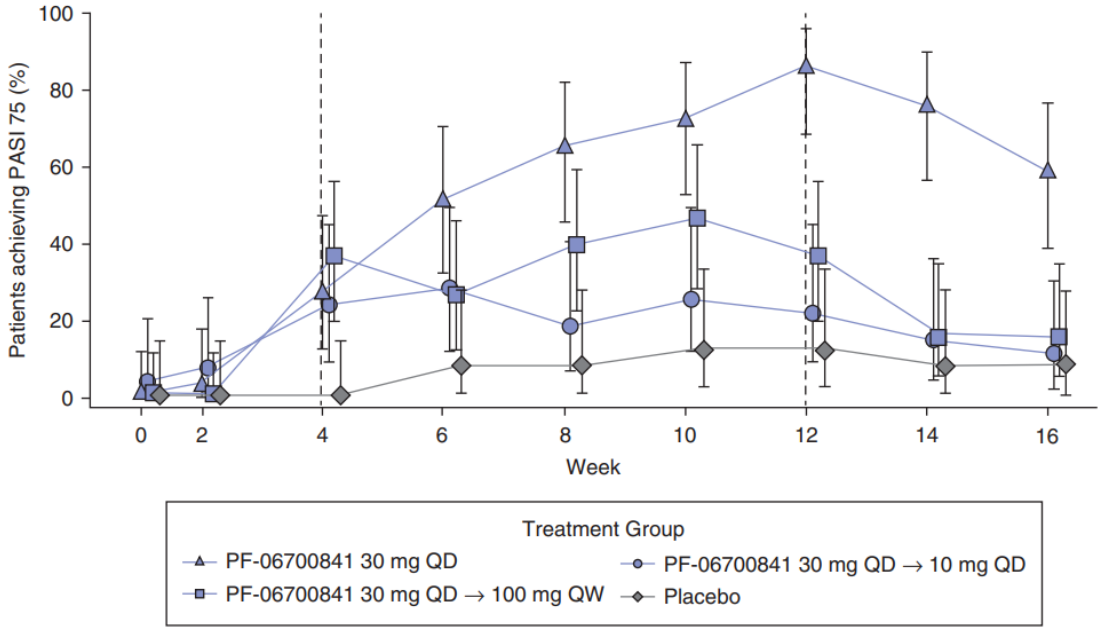
Morand E, et al. Annals of the Rheumatic Diseases 2022;81:209.

Key Data from Clinical Trials: Brepocitinib

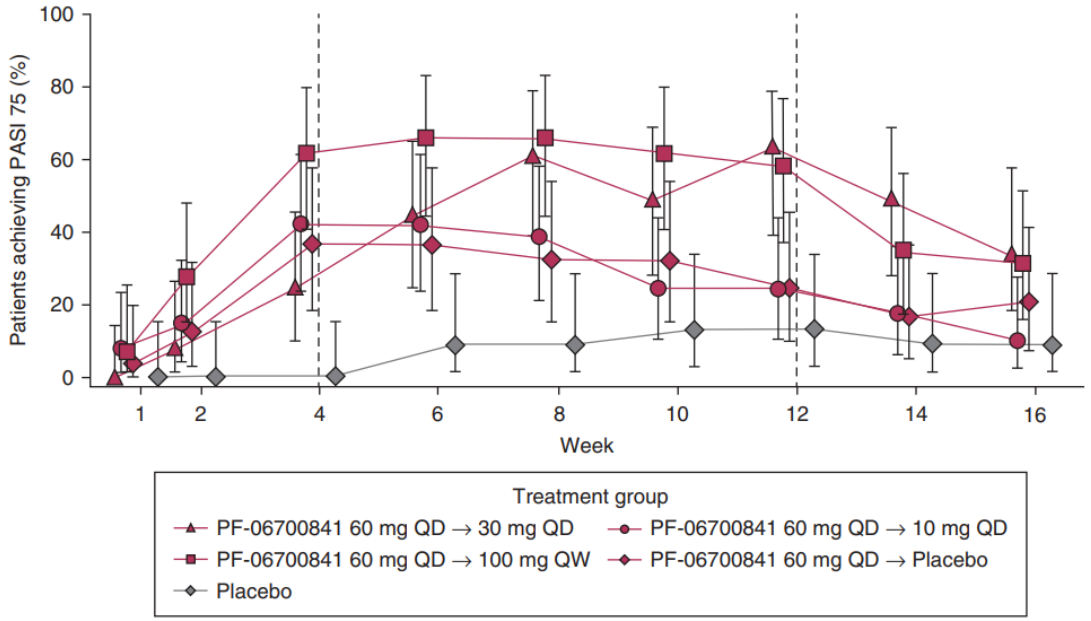
Brepocitinib (PF-06700841): Early Effectiveness Data in Psoriasis

Phase 2a clinical trial to evaluate brepocitinib 30 mg QD, 60 mg QD, or placebo (4-week induction), followed by 10 mg QD, 30 mg QD, 100 mg once weekly, or placebo (8-week maintenance)

PASI 75 Responses of Brepocitinib 30 mg QD Induction Dose



PASI 75 Responses of Brepocitinib 60 mg QD Induction Dose



Forman SB, et al. J Invest Dermatol. 2020 Dec;140(12):2359-2370.e5.

Brepocitinib (PF-06700841): Safety Outcomes in Psoriasis

	Treatment group								
	PF-06700841								
	60 to 30 mg QD	60 to 10 mg QD	60 mg QD to 100 mg QW	60 mg QD to placebo	30 mg QD	30 to 10 mg QD	30 mg QD to 100 mg QW	Placebo	Total
Number of patients evaluable for TEAEs	25	29	26	25	29	25	30	23	212
Number (%) of patients									
With TEAEs	19 (76.0)	21 (72.4)	18 (69.2)	18 (72.0)	21 (72.4)	16 (64.0)	23 (76.7)	13 (56.5)	149 (70.3)
With SAEs[1]	2 (8.0)	1 (3.4)	1 (3.8)	1 (4.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	5 (2.4)
With severe TEAEs	3 (12.0)	1 (3.4)	1 (3.8)	2 (8.0)	0 (0.0)	1 (4.0)	2 (6.7)	1 (4.3)	11 (5.2)
Discontinued from the study because of TEAEs[2]	2 (8.0)	4 (13.8)	1 (3.8)	2 (8.0)	0 (0.0)	2 (8.0)	2 (6.7)	0 (0.0)	13 (6.1)
With dose reduced or temporary discontinuation because of TEAEs	1 (4.0)	0 (0.0)	1 (3.8)	1 (4.0)	0 (0.0)	1 (4.0)	0 (0.0)	1 (4.3)	5 (2.4)

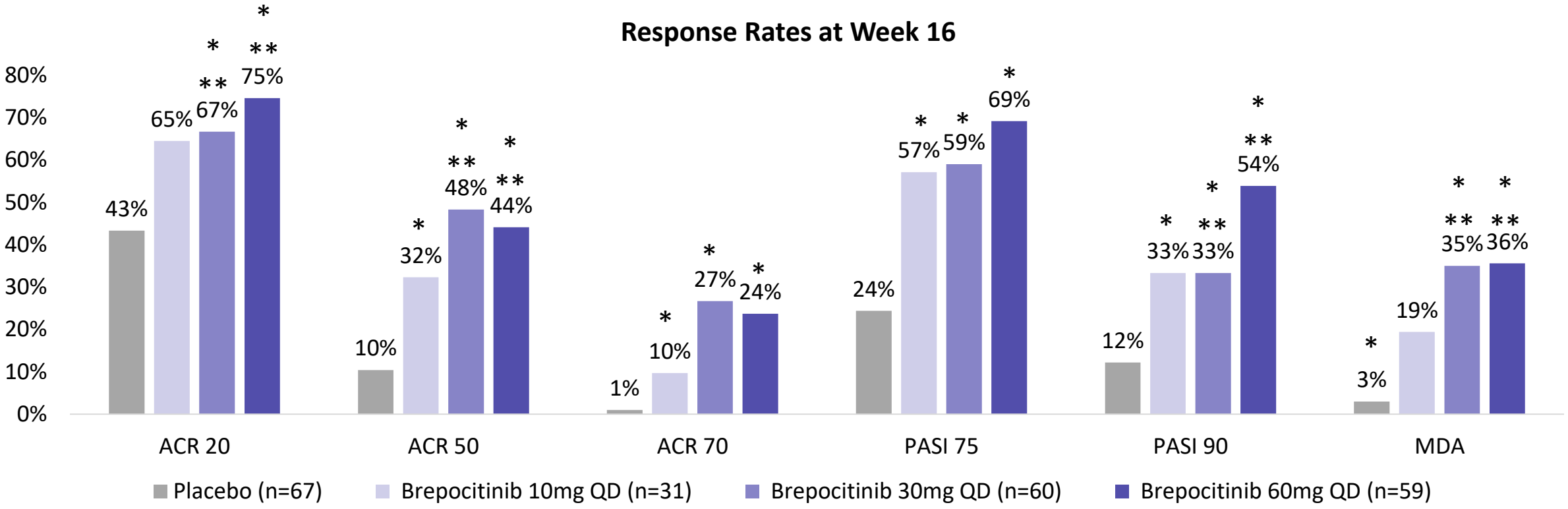
- **Most common all-causality TEAEs across brepocitinib treatment groups:**
  - Nasopharyngitis (28/189, 14.8%); upper respiratory tract infection (14/189, 7.4%); headache (14/189, 7.4%)
- **Most common treatment-related TEAEs across brepocitinib treatment groups :**
  - Headache (6/189, 3.2%); psoriasis (4/189, 2.1%); upper respiratory tract infection (3/189, 1.6%); nausea (3/189, 1.6%); fatigue (3/189, 1.6%)
- **13 all-causality discontinuations across brepocitinib treatment groups:**
  - 4 not related to treatment; 9 treatment-related
- **No major adverse cardiac events, including thromboembolic events, were reported during the stud**
- **No opportunistic infections were observed**
  - Herpes infection: No cases of herpes zoster were reported; 3 patients in the brepocitinib treatment groups experienced herpes simplex
- **Changes in laboratory parameter**
  - 1 case of increased blood creatine phosphokinase muscle/brain
  - 1 case of decrease from BL in serum eGFRcysin (patient with elevated serum creatine and preexisting kidney disease at BL who also reported a serious AE of anemia)
  - 4 cases of high serum creatinine

AE = adverse event; BL = baseline; eGFRcys=cystatin C-based estimated glomerular filtration rate; TEAE = treatment emergent adverse events.

Forman SB, et al. J Invest Dermatol. 2020 Dec;140(12):2359-2370.e5.

Brepocitinib (PF-06700841): Effectiveness in Psoriatic Arthritis

Phase 2b trial to compare the efficacy and safety of brepocitinib (10, 30, and 60 mg QD) vs placebo in patients with active PsA for 52-weeks (with an initial 16-week initial dose)



*** 1-sided raw p-value for the treatment comparison vs placebo was <0.05**

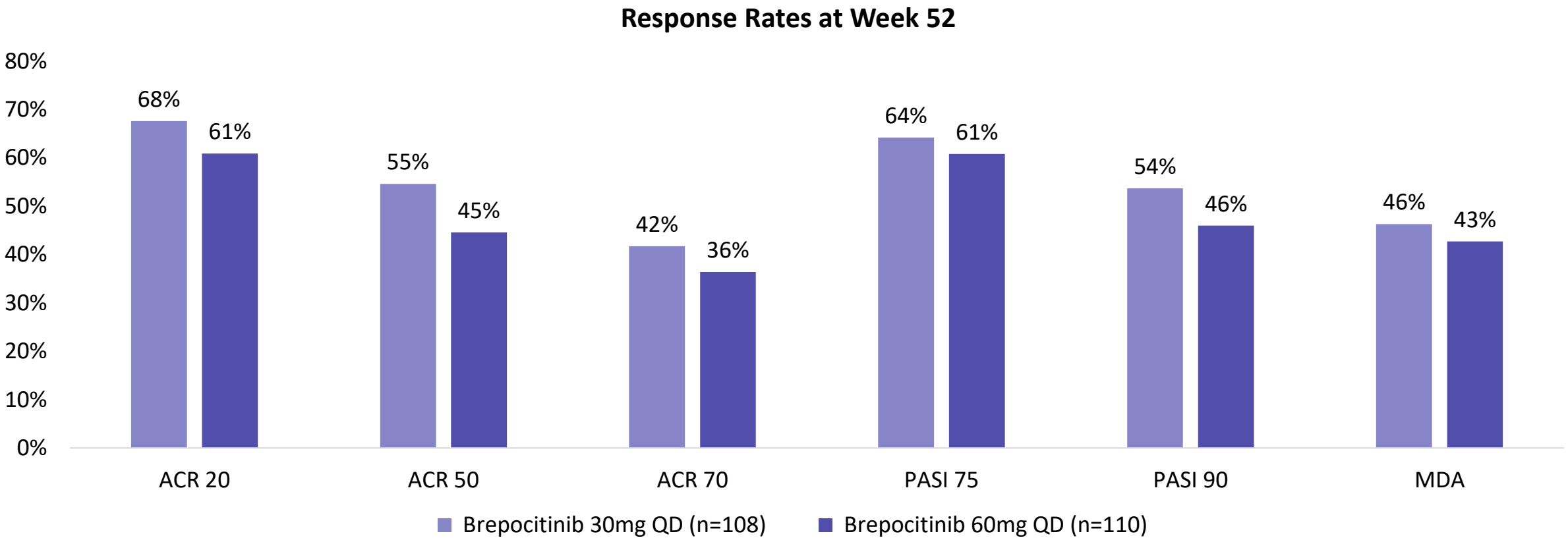
**** Treatment group showed statistically significant treatment effect vs placebo under the pre-specified study testing procedure.**

MDA = minimal disease activity

Mease P, et al. Abstract 0488. Presented at ACR Convergence 2021. November 5-9, 2021. All Virtual.

Brepocitinib (PF-06700841): Long-Term Effectiveness in PsA

Extension of phase 2b with patients advancing to brepocitinib 30 or 60 mg QD from Week 16 to 52



Mease P, et al. Abstract 0488. Presented at ACR Convergence 2021. November 5-9, 2021. All Virtual.

Brepocitinib (PF-06700841): Safety Outcomes in PsA

Treatment Emergent AEs and AEs of Special Interest from the PsA Phase 2 Trial (Up to 52 Weeks)

	Up to Week 16 (initial dose)					After Week 16	
Number (%) of pts	PBO (n=67)	Brepocitinib				Brepocitinib	
		10 mg QD (n=31)	30 mg QD (n=60)	60 mg QD (n=60)	Total (n=151)	30 mg QD (n=108)	60 mg QD (n=110)
Any AE	32 (47.8)	14 (45.2)	33 (55.0)	40 (66.7)	87 (57.6)	50 (46.3)	55 (50.0)
SAE	1 (1.5)	0 (0.0)	3 (5.0)	1 (1.7)	4 (2.6)	7 (6.5)	1 (0.9)
AE leading to discontinuation of study drug	3 (4.5)	0 (0.0)	2 (3.3)	3 (5.0)	5 (3.3)	5 (4.6)	10 (9.1)
Deaths	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Infections and infestations (SOC)	16 (23.9)	9 (29.0)	21 (33.0)	21 (35.0)	51 (33.8)	19 (17.6)	27 (24.6)
Serious infections	0 (0.0)	0 (0.0)	2 (3.3)	0 (0.0)	2 (1.3)	3 (2.8)	1 (0.9)
Adjudicated opportunistic infections	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.9)	1 (0.9)
Herpes zoster/varicella	0 (0.0)	1 (3.2)	1 (1.7)	0 (0.0)	2 (1.3)	1 (0.9)	1 (0.9)
Active tuberculosis	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
COVID-19 infections	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	6 (5.6)	8 (7.3)
Neoplasms, benign, malignant, and unspecified (SOC)	0 (0.0)	0 (0.0)	0 (0.0)	2 (3.3)	2 (1.3)	1 (0.9)	0 (0.0)
Embolic and thrombotic events	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

AE = adverse events; SAE = serious adverse events; SOC = system organ class

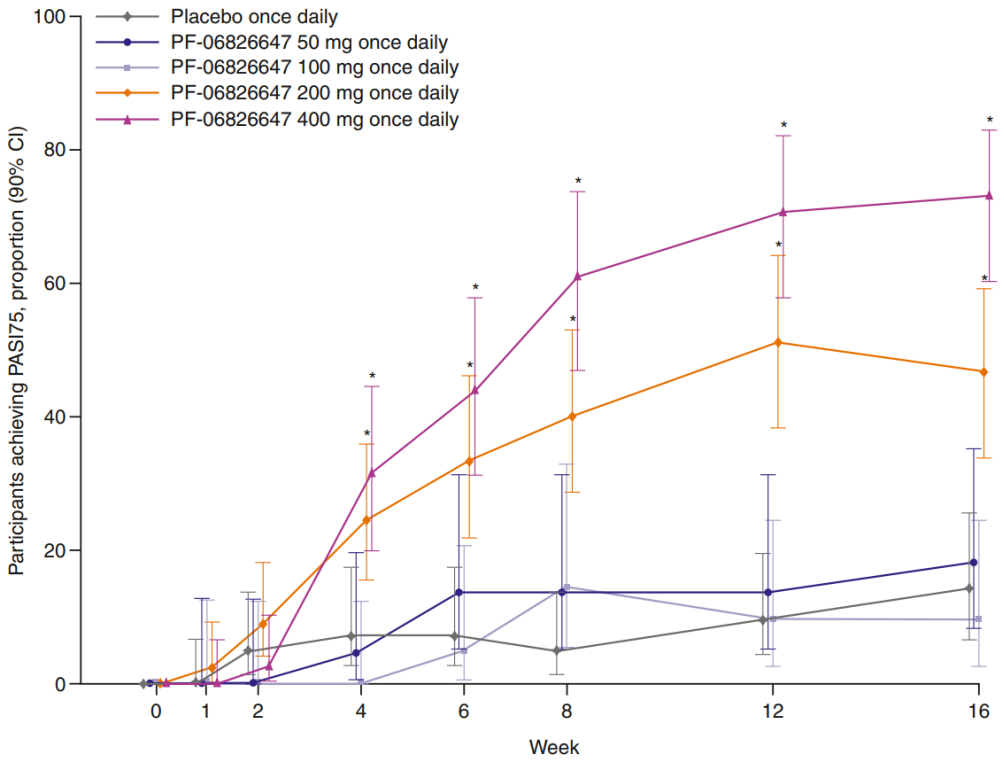
Mease P, et al. Abstract 0488. Presented at ACR Convergence 2021. November 5-9, 2021. All Virtual.

Key Data from Clinical Trials: Ropsacitinib

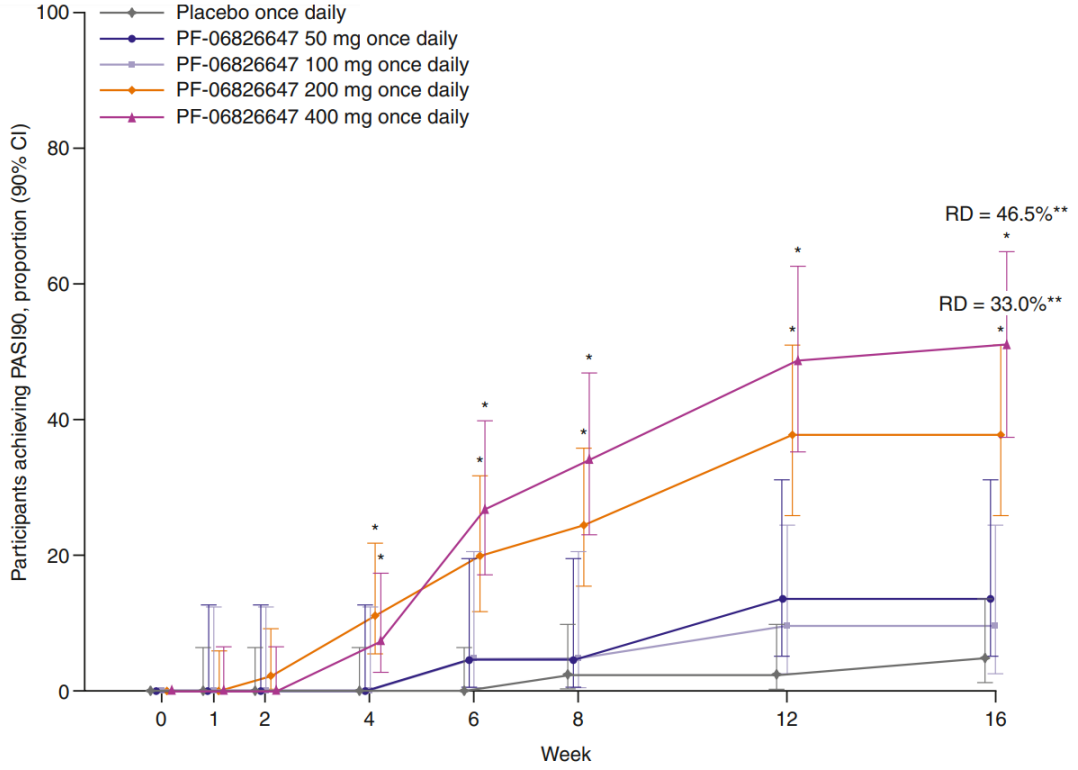
Ropsacitinib (PF-06826647): Clinical Efficacy in Psoriasis

Phase 2b clinical trial to evaluate ropsacitinib (50mg, 100mg, 200mg and 400mg QD) vs placebo for 16 weeks, then 200 or 400 mg for 24 weeks in patients with moderate to severe PsO

PASI 75 Response



PASI 90 Response



Tehlirian C, et al. J Am Acad Dermatol. 2022 Aug;87(2):333-342.

Ropsacitinib (PF-06826647): Safety Outcomes in Psoriasis

Number of participants, n (%)	Placebo (n = 45)	PF-06826647 50 mg once daily (n = 22)	PF-06826647 100 mg once daily (n = 23)	PF-06826647 200 mg once daily (n = 45)	PF-06826647 400 mg once daily (n = 43)	Total (N = 178)
TEAEs	23 (51.1)	13 (59.1)	16 (69.6)	28 (62.2)	29 (67.4)	109 (61.2)
Mild	14 (31.1)	10 (45.5)	6 (26.1)	18 (40.0)	17 (39.5)	65 (36.5)
Moderate	8 (17.8)	3 (13.6)	9 (39.1)	18 (17.8)	9 (20.9)	37 (20.8)
Severe*	1 (2.2)	0 (0.0)	1 (4.3)	2 (4.4)	3 (7.0)	7 (3.9)
SAE†	0 (0.0)	1 (4.5)	0 (0.0)	1 (2.2)	0 (0.0)	2 (1.1)
Discontinued due to TEAEs	1 (2.2)	0 (0.0)	0 (0.0)	5 (11.1)	3 (7.0)	9 (5.1)
TRAEs	4 (8.9)	0 (0.0)	4 (17.4)	11 (24.4)	8 (18.6)	27 (15.2)
Mild	3 (6.7)	0 (0.0)	2 (8.7)	6 (13.3)	4 (9.3)	15 (8.4)
Moderate	1 (2.2)	0 (0.0)	2 (8.7)	3 (6.7)	3 (7.0)	9 (5.1)
Severe‡	0 (0.0)	0 (0.0)	0 (0.0)	2 (4.4)	1 (2.3)	3 (7.1)
Treatment-related SAE§	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.2)	0 (0.0)	1 (0.6)
Laboratory abnormalities, n/N (%)‖						
Hemoglobin (low [<0.8×LLN])	0/44 (0.0)	0/22 (0.0)	0/23 (0.0)	2/45 (4.4)	3/43 (7.0)	5/177 (2.8)
Reticulocyte count (low [<0.5×LLN])	0/44 (0.0)	0/22 (0.0)	0/21 (0.0)	0/42 (0.0)	2/41 (4.9)	2/170 (1.2)
Reticulocyte count (high [>1.5×ULN])	0/44 (0.0)	0/22 (0.0)	0/21 (0.0)	0/42 (0.0)	2/41 (4.9)	2/170 (1.2)
Total neutrophil count (low [<0.8×LLN])	1/45 (2.2)	0/20 (0.0)	2/21 (9.5)	3/38 (7.9)	4/39 (10.3)	10/163 (6.1)
Total neutrophil count (high [>1.2×ULN])	3/45 (6.7)	1/20 (5.0)	1/21 (4.8)	2/38 (5.3)	2/39 (5.1)	9/163 (5.5)
Total lymphocyte count (low [<0.8×LLN])	0/45 (0.0)	0/22 (0.0)	0/22 (0.0)	1/45 (2.2)	1/43 (2.3)	2/177 (1.1)
Total lymphocyte count (high [>1.2×ULN])	0/45 (0.0)	0/22 (0.0)	1/22 (4.5)	1/45 (2.2)	1/43 (2.3)	3/177 (1.7)
Platelet count (low [<0.5×LLN])	0/42 (0.0)	0/22 (0.0)	0/21 (0.0)	0/42 (0.0)	1/41 (2.4)	1/168 (0.6)
Platelet count (high [>1.75×ULN])	0/42 (0.0)	0/22 (0.0)	0/21 (0.0)	0/42 (0.0)	0/41 (0.0)	0/168 (0.0)
AST (high [>3.0×ULN])	1/43 (2.3)	0/20 (0.0)	1/23 (4.3)	0/40 (0.0)	0/36 (0.0)	2/162 (1.2)
ALT (high [>3.0×ULN])	1/40 (2.5)	0/18 (0.0)	0/21 (0.0)	0/38 (0.0)	0/30 (0.0)	1/147 (0.7)
Creatinine (high [>1.3×ULN])	0/45 (0.0)	0/21 (0.0)	0/23 (0.0)	1/45 (2.2)	1/42 (2.4)	2/176 (1.1)
Triglycerides (high [>1.3×ULN])	1/39 (2.6)	0/20 (0.0)	0/23 (0.0)	0/43 (0.0)	3/43 (7.0)	4/168 (2.4)
CPK (high [>2.0×ULN])	3/42 (7.1)	3/20 (15.0)	2/22 (9.1)	9/42 (21.4)	15/40 (37.5)	32/166 (19.3)

- **Up to week 16, most common TEAEs:**
  - Nasopharyngitis
  - Upper respiratory tract infection
  - Increased blood pressure
- **7 participants experienced severe TEAEs, of which 3 were treatment related:**
  - Thrombocytopenia
  - Increased blood CPK
  - Hypertension
- **2 participants experienced serious AEs, of 3 were treatment related (200mg):**
  - Chest pain
  - Hypertension
  - Neurologic symptoms
- **9 participants discontinued the study up to week 16 due to TEAEs, 7 were treatment-related**
- **No treatment-related clinically detectable findings in ECG, adjudicated cardiovascular events, or deaths occurred in the study**

ALT = alanine aminotransferase; AST = aspartate transaminase; CPK = creatine phosphokinase; ECG = electrocardiogram; LLN = Lower Limit of Normal; TEAE = treatment-emergent AEs; TRAEs = Treatment-related adverse events SAE = serious adverse events; ULL = Upper Limit of Normal.

Tehlirian C, et al. J Am Acad Dermatol. 2022 Aug;87(2):333-342.

Wrap Up

Summary:

- **Reviewed the mechanism of action of TYK2 signaling across rheumatic diseases**

- **Reviewed the clinical data of emerging therapies targeting the TYK2 pathway**