The Role of IL-17/IL-23 Across Rheumatic 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

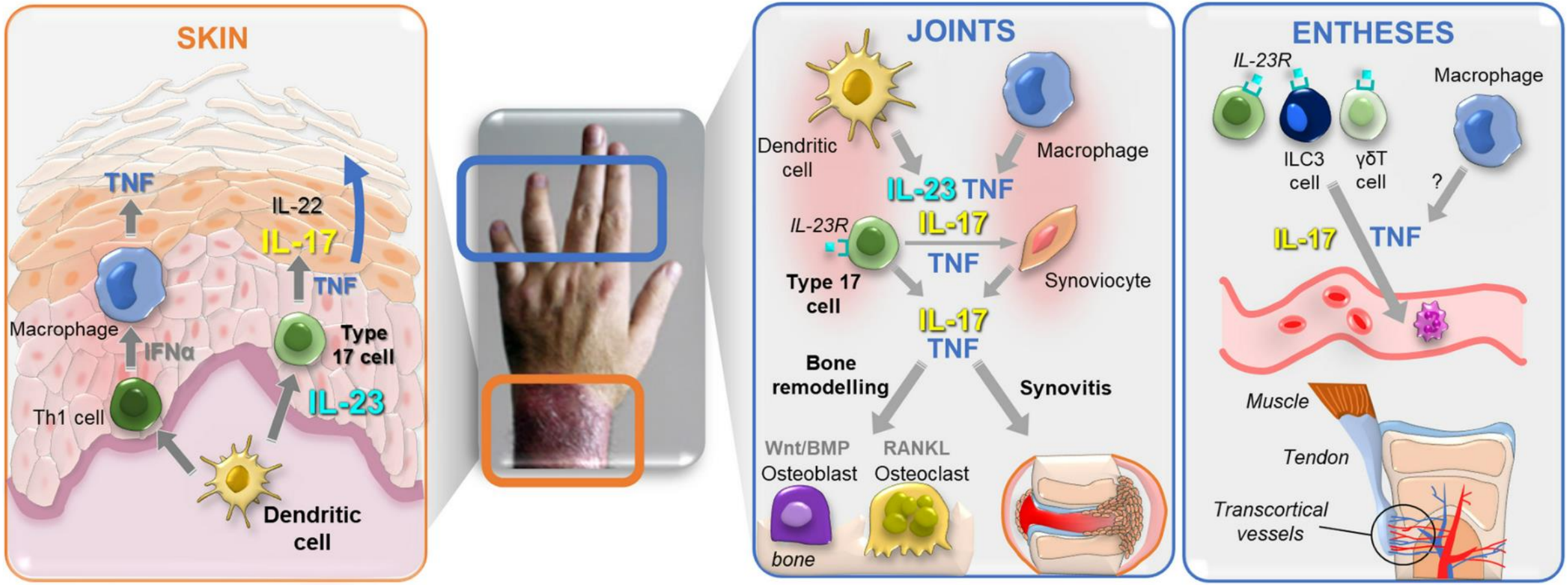
Learning Objectives

- **Review the mechanism of action of IL-17/IL-23 signaling across rheumatic diseases**
- **Review clinical data of new and emerging therapies targeting the IL-12 and IL-23 pathway**

IL = interleukin.

IL-17/IL-23 Signaling Pathways and Associated Treatment Targets

Multiple Pathways Involved in Skin and Joint Inflammation



Scher JU, et alArthritis Rheumatol. 2021 Sep;73(9):1574-1578.

Dual Action of IL23 in Skin Pathogensis

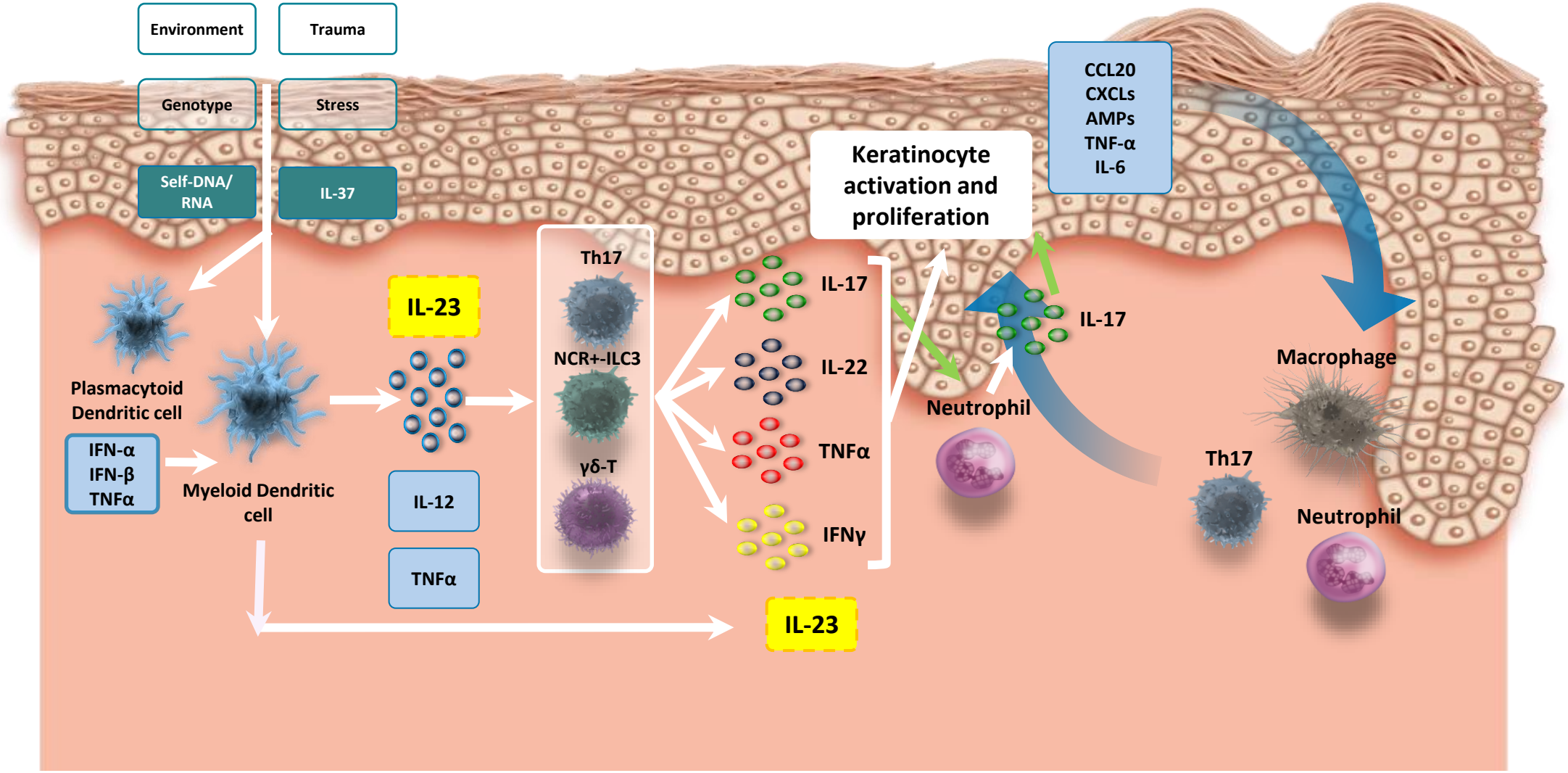
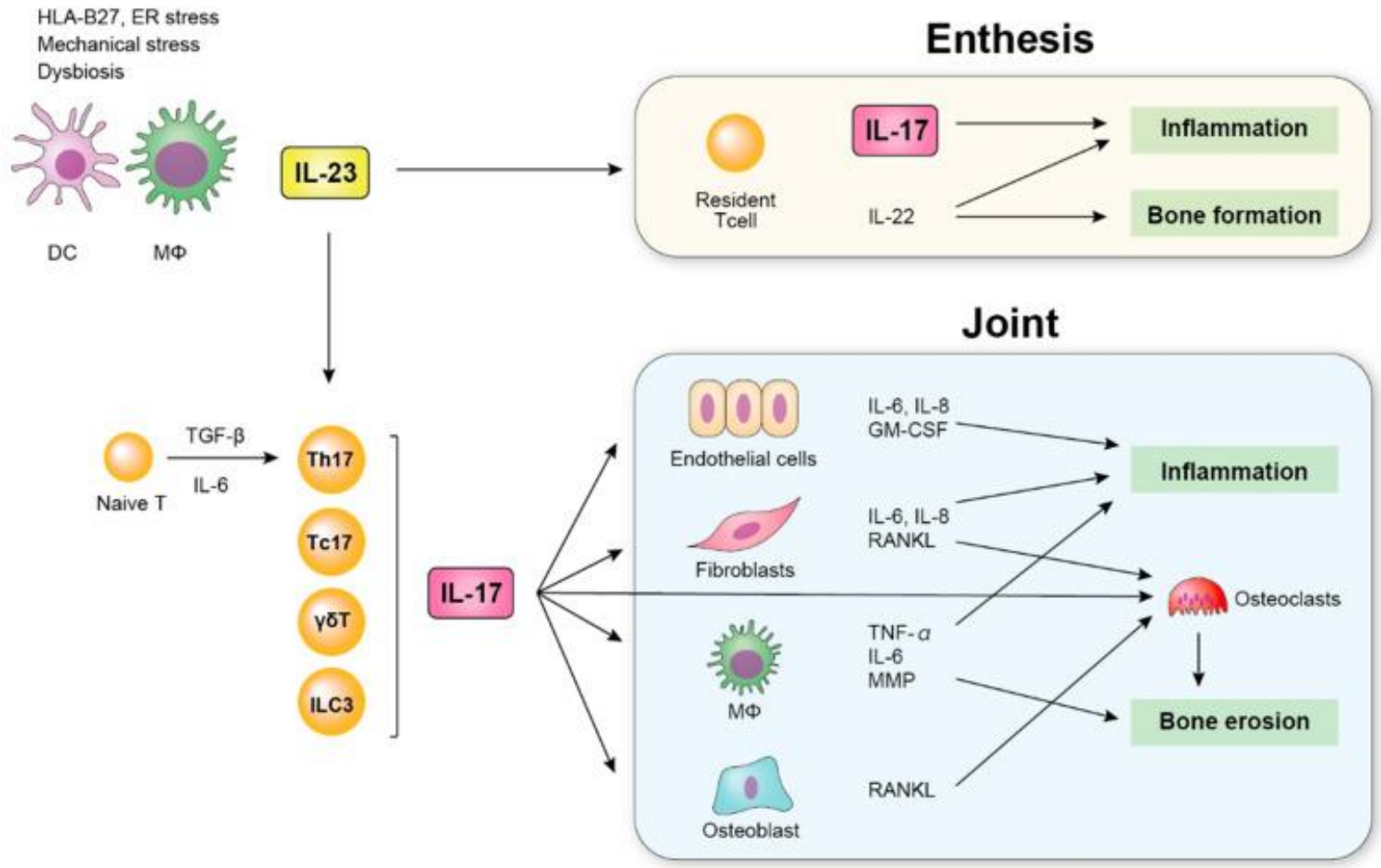


Figure adapted from: Nestle FO et al, N Engl J Med 2009;361:496–5092. Nograles KE et al, J Allergy Clin Immunol 2009;123:1244–52. Lowes MA et al, Nature 2007;445(7130):866–73. Hawkes JE, et al. J Allergy Clin Immunol 2017;140:645–53. Kim J, Krueger JG. Dermatol Clin 2015;33:13–23

The IL-17 and IL-23 Pathway in Spondyloarthritis Pathogenesis

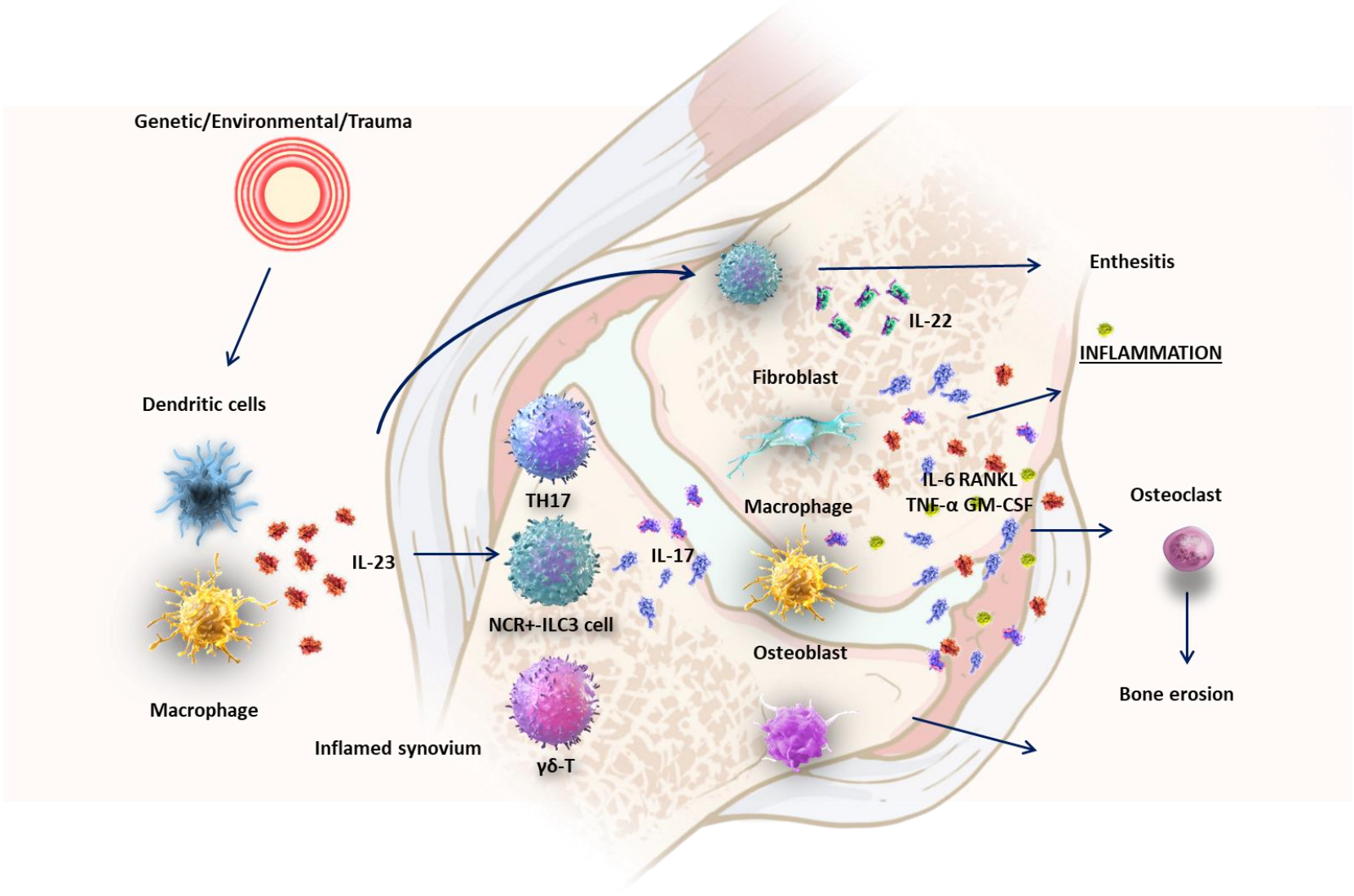
- **Dendric cells and macrophages produce IL-23**
- **IL-23 induces the production of IL-17 by various cells**
- **IL-17 upregulates production of inflammatory cytokines**
  - Enthesis
  - Joint



DC = dendritic cell; MΦ = macrophages; GM-CSF = Granulocyte macrophage colony-stimulating factor; RANKL = Receptor activator of nuclear factor kappa-B ligand; MMP = matrix metalloproteinases .

Tsukazaki H, et al. Int J Mol Sci. 2020 Sep 3;21(17):6401

Dual Action of IL-23 in Joint Pathogenesis



- **Joint pathogenesis due to genetic and environmental factors**
- **Triggers promote synovial angiogenesis**
  - Facilitates immune infiltration of synovial tissues
  - Influx of activated immune cells releases cytokines and increases inflammation
- **Dendritic cells are immature in the synovial fluid of PsA**
  - Promote downstream elevation of TNF-α, INF-γ, and IL-235
- **Proinflammatory mediators activate resident cells in the joint and at the enthesis**
  - Secrete more proinflammatory mediators
    - Lead to cartilage degradation, bone erosion, and joint damage
    - Recruit more immune cells, creating a persistent response

Sakkas LI, et al. Autoimmun Rev. 2017;16(1):10-15;Ritchlin CT, et al. N Engl J Med. 2017;376(10):957-970; Ritchlin Ctet al. J Clin Invest. 2003;111(6):821-831; Luo G, et al. Mol Med Rep. 2018;17(5):6605-6611; Veale DJ, et al, Lancet. 2018;391(10136):2273-2284; Hawkes JE, et al. J Allergy Clin Immunol. 2017;140(3):645-653; Chan TC, et al. Ther Adv Chronic Dis. 2018;9(5):111-119; Schon MP, et al. Front Immunol. 2018;9:1323; Machado A, et al. Psoriasis (Auckl). 2018;8:83-92; Blauvelt A, et al. Clinic Rev Allerg Immunol. 2018;55(3):379-390.

Aberrant T-Cell Signaling and IL-17 Production in SLE Pathogenesis

Abnormal T-cell signaling

↓

Overproduction of IL-17

↓

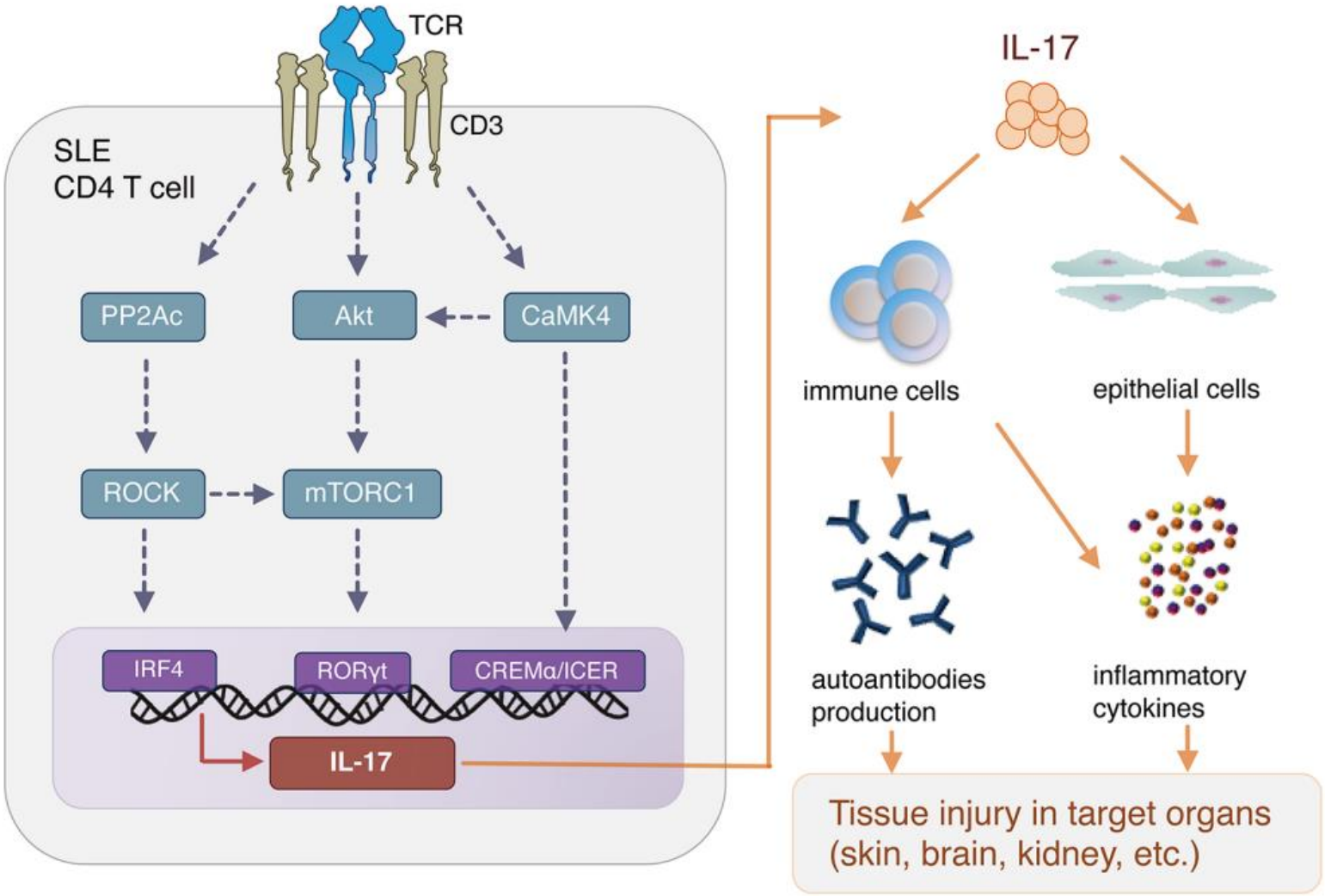
Immune and other cell activation

↓

Autoantibody and proinflammatory cytokine production

↓

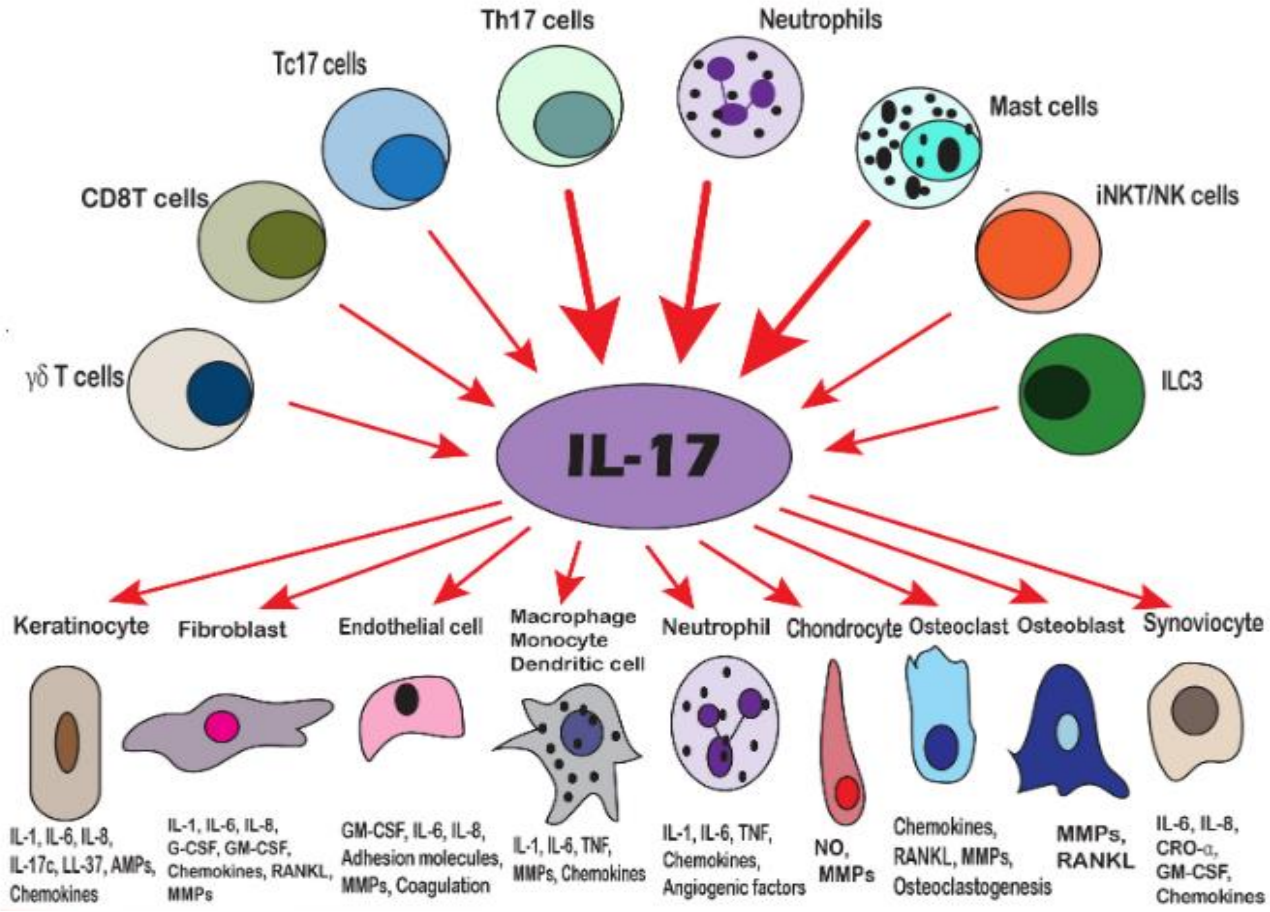
Organ damage



SLE, systemic lupus erythematosus; TCR, T cell receptor; PP2Ac, Protein phosphatase 2A catalytic subunit; CaMK4, Calcium/calmodulin-dependent protein kinase IV; ROCK, Rho-associated protein kinase; CREB, cAMP response element binding protein; IRF4, interferon regulatory factor 4; CREM, cAMP response element modulator; mTORC1, mammalian target of rapamycin complex

Koga T, et al. Front Immunol. 2021 Feb 1;11:624971.

IL-17 is Involved in Multiple Autoimmune and Inflammatory Diseases



- **Recruitment of immune cells and chronic inflammation**
  - Neurodegeneration → MS
  - Damage of GI tract → IBD
  - Keratinocyte hyperproliferation → PsO
  - Thrombosis → Behcet disease, SLE, RA
  - Cartilage damage → SLE, RA
  - Bone erosion → SLE, RA
  - Tissue damage → periodontitis

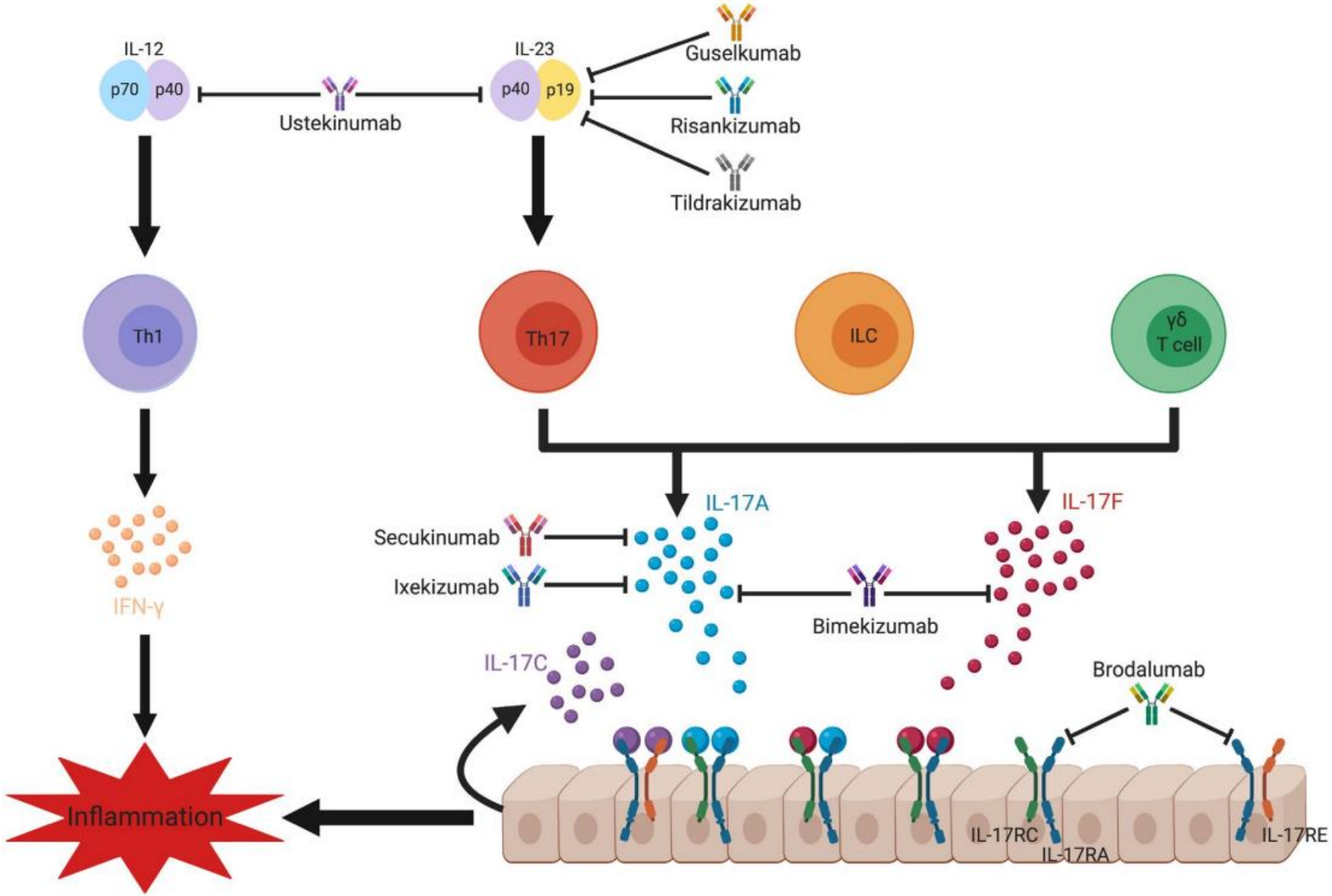
MS: multiple sclerosis; IBD: inflammatory bowel disease; SLE: systemic lupus erythematosus; RA: rheumatoid arthritis; MMPs: matrix metalloproteinases; G-CSF; granulocyte colony-stimulating factor; NK: natural killer; iNKT: Invariant natural killer T cells; ILC3: group 3 innate lymphoid cells; IL: interleukin; TNF: tumor necrosis factor; GM-CSF: granulocyte–macrophage colony-stimulating factor.

Berry SPD, et al. Int Immunopharmacol. 2022 Jan;102:108402.

POLLING QUESTION

- **Which of the following biologic therapies inhibit IL-17A & IL-17F?**
  - A. Bimekizumab
  - B. Ixekizumab
  - C. Risankizumab
  - D. Secukinumab
  - E. Ustekinumab

Mechanisms of Action of IL-17/-23 Inhibitors



Fletcher JM, et al. Clin Exp Immunol. 2020 Aug;201(2):121-134.

Approved and Late-Stage IL-17/-23 Inhibitors

Agent	Target	Indications / Phase
Ustekinumab	IL-12 / IL-23	• PsO in >6yo (approved) • PsA in >18yo (approved) and >6yo (under FDA review)
Guselkumab	IL-23	• PsO in >18yo (approved) and >6yo (phase 3) • PsA >18yo (approved)
Risankizumab	IL-23	• PsO in >18yo (approved) • PsA >18yo (approved)
Secukinumab	IL-17A	• PsO in >6yo (approved) • PsA >2yo (approved) • AS in >18yo (approved) • nr-axSpA in >18yo (approved) • ERA in >4yo (approved) • HS (phase 3) • LN (phase 3) • GCA (phase 3)
Ixekizumab	IL-17A	• PsO in >6yo (approved) • PsA >18yo (approved) • AS in >18yo (approved) • nr-axSpA in >18yo (approved) • JIA (phase 3)
Brodalumab	IL-17RA	• PsO in >18yo (approved)
Bimekizumab	IL-17A & IL-17F	• PsO (under FDA review) • PsA (phase 3) • axSpA (phase 3) • HS (phase 3)

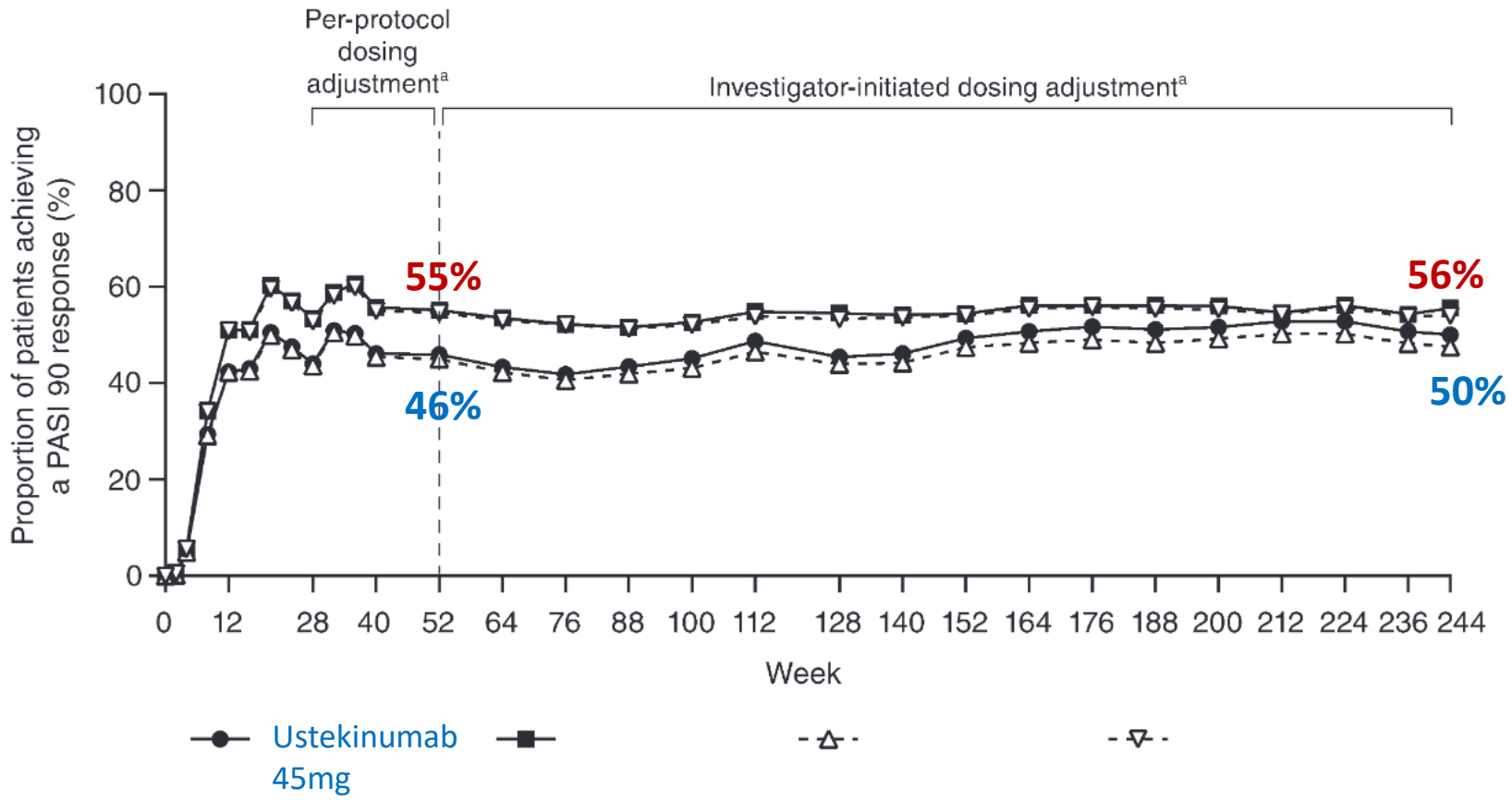
PsA = psoriatic arthritis; AS = ankylosing spondylitis; nr-axSpA = non-radiographic axial spondyloarthritis; ERA = enthesitis-related arthritis; LN = lupus nephritis; GCA = giant cell arteritis; HS = hidradenitis suppurativa.

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 of IL-17/-23 Inhibitors Across Rheumatic Conditions

Ustekinumab (IL-12 / IL-23): Efficacy in Psoriasis After 5 Years

PHOENIX 2 evaluated ustekinumab 45 mg and 90 mg through 5 years of follow-up in patients with moderate to severe psoriasis



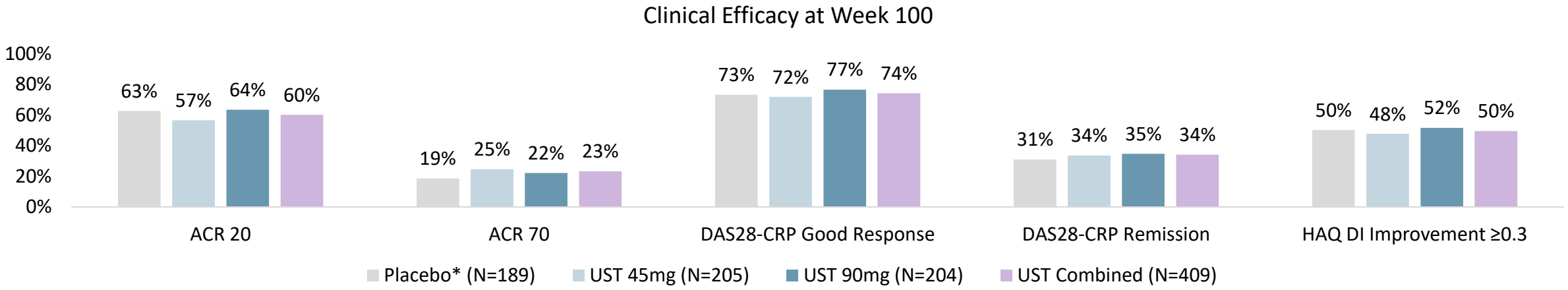
- **Higher proportion of patients achieved a PASI 75 response, and were maintained through the 5-year follow-up period**
  - 71% for UST 45mg
  - 79% for UST 90mg
- **Results were similar for the LOCF analyses**
  - inclusion/exclusion of patients who discontinued for reasons unrelated to efficacy did not alter results
- **Dosing adjustments**
  - 20% early adjusters
  - 31% late adjusters
  - 49% non-adjusters
- **70% patient retention through year 5**

LOCF = last-observation-carried-forward; UTS = ustekinumab.

Langley RG, et al. J Dermatol. 2015;172(5):1371-83.

Ustekinumab (IL-12 / IL-23): Efficacy in Psoriatic Arthritis after 2 Years

PSUMMIT 1 study evaluated the efficacy and safety of ustekinumab through 2 years in adult patients with active PsA, despite prior DMARD or NSAID therapy



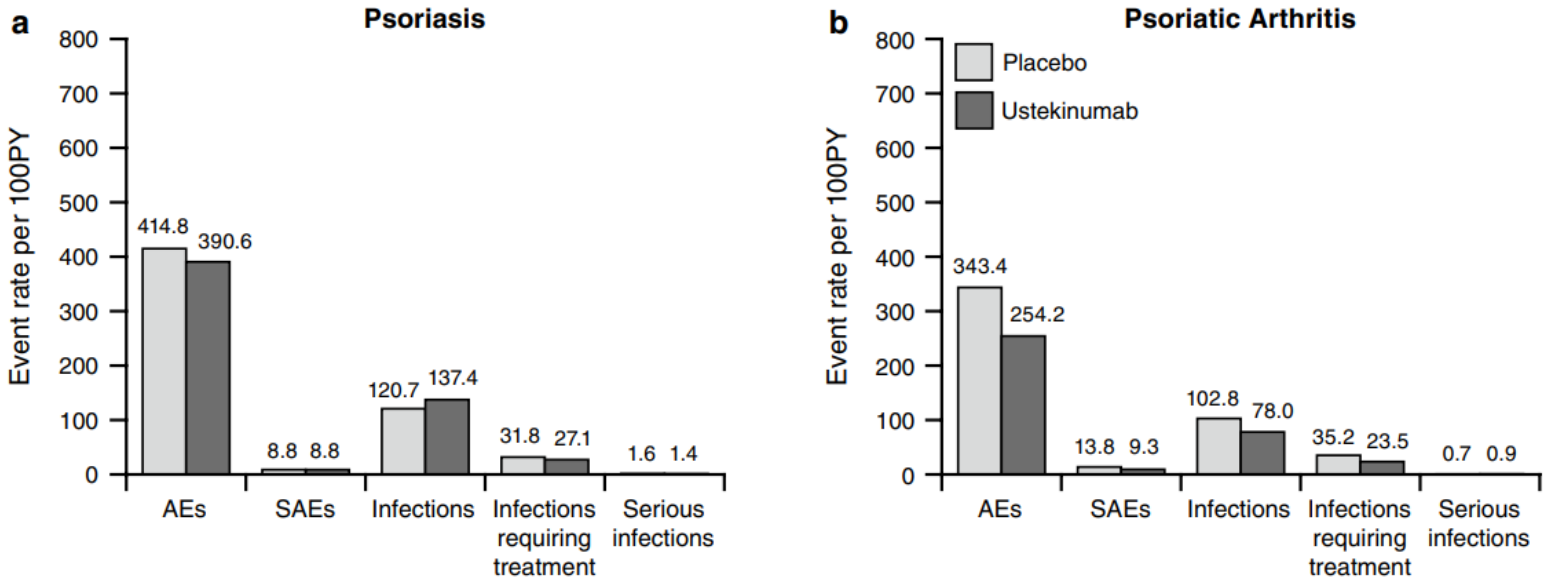
Measure	Placebo*		UST 45mg		UST 90mg		UST Combined	
	Baseline	Week 100	Baseline	Week 100	Baseline	Week 100	Baseline	Week 100
Patients with ≥1 dactylitis digit	87	31	101	29	99	27	200	56
Patients with enthesitis	128	62	142	58	154	61	296	117
SF-36 PCS score (change from BL)	-	4.8	-	5.1	-	6.4	-	5.3
DLQI score (change from BL)	-	-6	-	-5	-	-6	-	-5
PsA-m total SHS score (change from BL)	-	2.26	-	0.95	-	1.18	-	1.07

CRP= C-reactive protein; DAS28= Disease Activity Score in 28 joints; DLQI = Dermatology Life Quality Index; DMARD = disease-modifying antirheumatic drugs; HAQ-DI = Health Assessment Questionnaire disability index; NSAID = non-steroidal anti-inflammatory drugs; PsA-m = PsA modified; SHS = Sharp/van der Heijde score; SF-36 PCS = Short Form Physical Component Summary.

Kavanaugh A, et al. Arthritis Care Res (Hoboken). 2015 Dec;67(12):1739-49.

Ustekinumab (IL-12 / IL-23): Pooled Safety Analysis

Incidence Rates/100 PYs Among Patients Treated ≤1year in Phase II/III Studies



- Low occurrence of opportunistic infections and tuberculosis
- Comparable incidence of serious MACEs through year 1 among patients receiving ustekinumab (0.5) and placebo (0.3)
- Low and comparable incidences of malignancies were observed through year 1 among ustekinumab-treated patients (NMSC = 0.4; other=0.4) and placebo-treated patients (NMSC=0.6, other=0.2)
- No serious anaphylactic reactions or serum sickness-like reactions to ustekinumab were observed
- Serious neurological disorders were rare

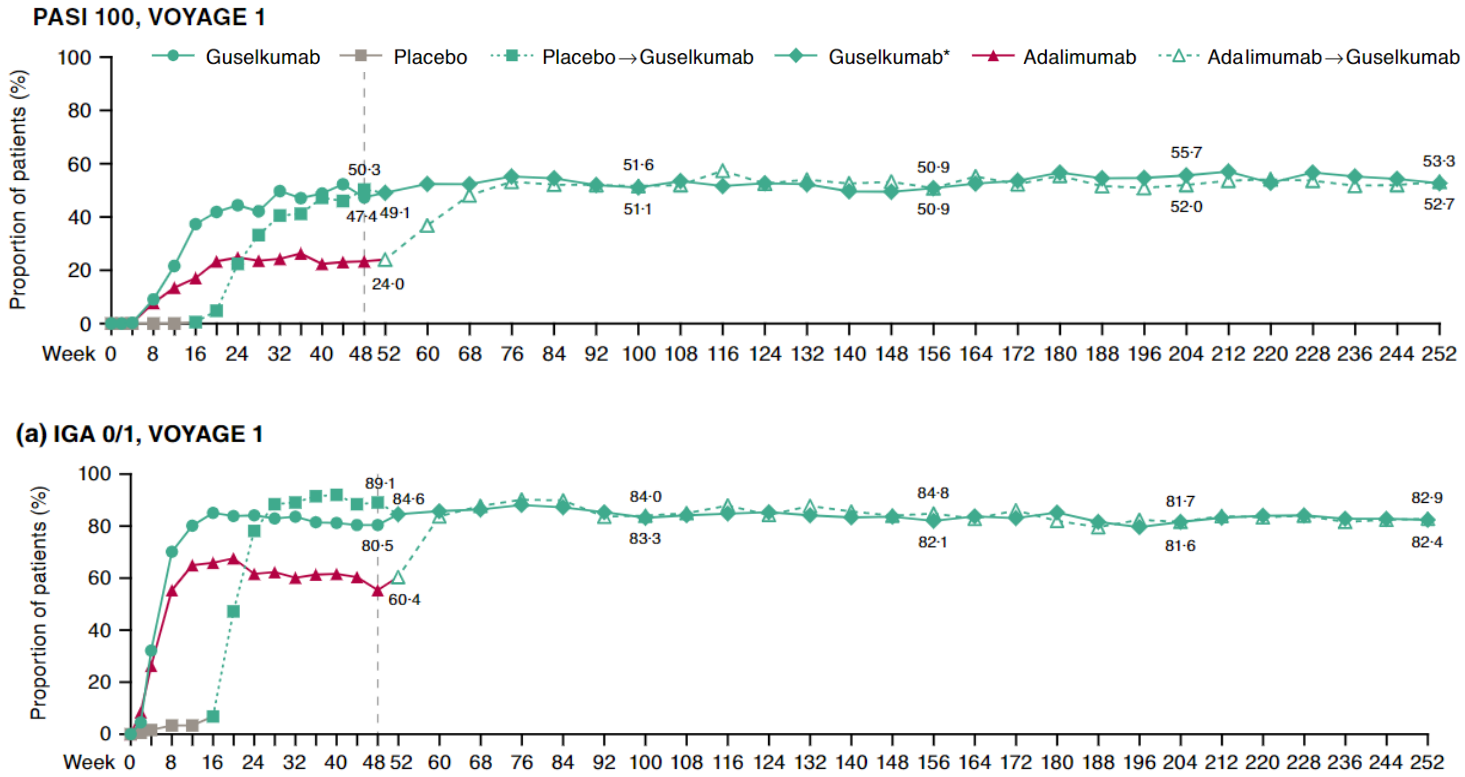
No dose-related or cumulative toxicity was observed with increasing duration of ustekinumab exposure for up to 5 years

AEs = adverse events; SAEs= serious adverse events; MACE = major adverse cardiovascular event; NMSC = non-melanoma skin cancer; PY = patient years

Ghosh S, et al. Drug Saf. 2019 Jun;42(6):751-768; Papp KA, et al. Br J Dermatol. 2013 Apr;168(4):844-54.

Guselkumab (IL-23): 5-Year Efficacy and Safety in Psoriasis

VOYAGE 1 and 2 evaluated were placebo- and adalimumab comparator-controlled trials of guselkumab in moderate-to-severe psoriasis. VOYAGE 1 included crossover to adalimumab at week 52.



Comparable long-term results were observed in VOYAGE 2 across the different efficacy and health-related quality of life measures analyzed

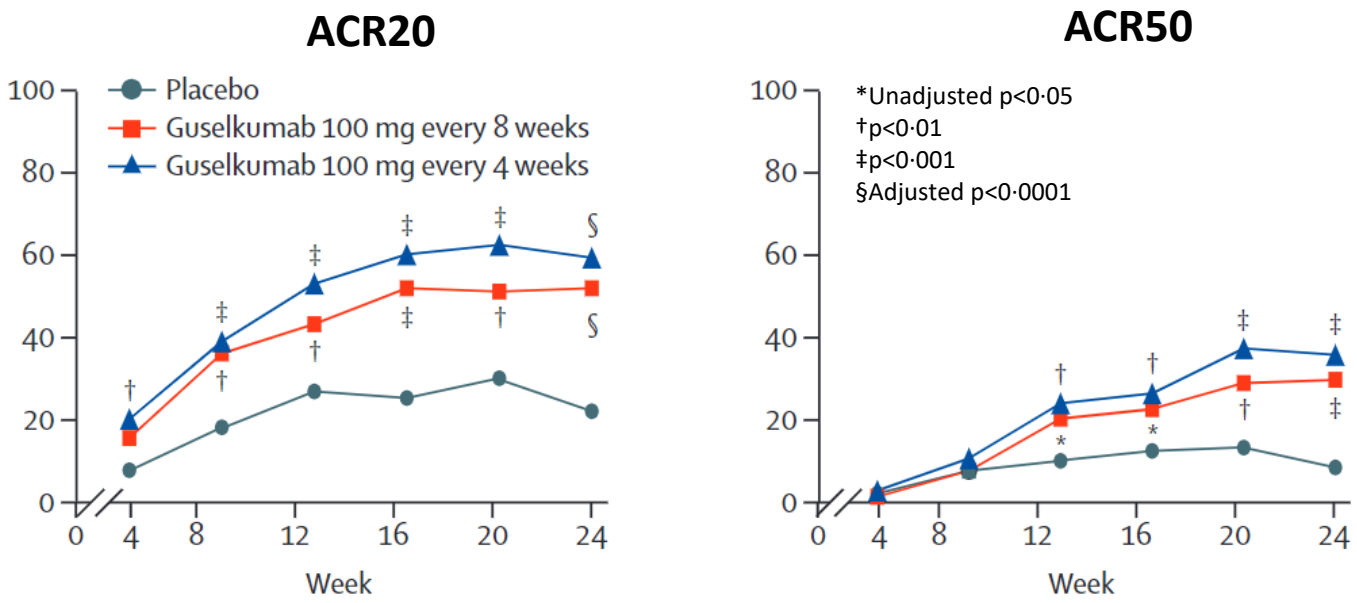
- **In VOYAGE 1, DLQI 0/1 scores were maintained through year 5**
  - Week 100: 75.2%
  - Week 252: 72.7%
- **In VOYAGE 2, SF-36 PCS ≥ 5-point improvements were maintained across both arms through year 5**
  - GUS: 46%
  - ADA -> GUS: 40%
- **Incidence of AEs in GUS-treated patients per 100PY through year 5**
  - AEs = 149
  - Serious AEs = 5.01
  - AEs leading to discontinuation = 1.45
  - Infections = 60.61
  - Serious infections = 0.85
  - Malignancies = 0.74
  - MACE = 0.29
- **No increase in event rates was observed with longer duration of GUS exposure over time based on annual assessments**

IGA 0/1 = Investigator's Global Assessment score of cleared or minimal psoriasis; DLQI 0/1 = Dermatology Life Quality Index (DLQI) scores of 0 or 1; ADA = adalimumab; GUS = guselkumab; MACE = major adverse cardiovascular event; PCS = Physical Component Summary

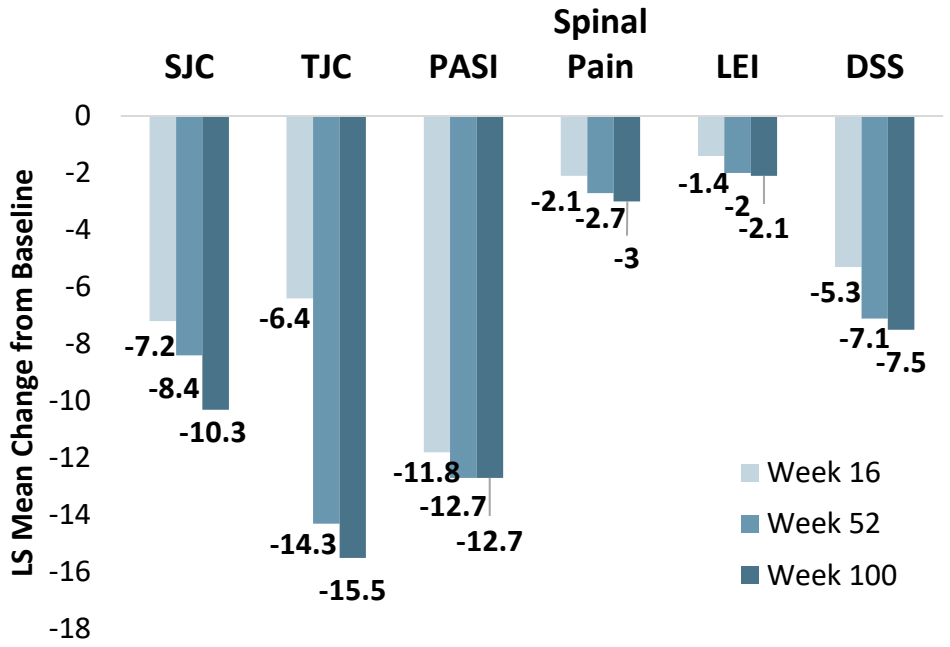
Reich K, et al. Br J Dermatol. 2021 Dec;185(6):1146-1159; Blauvelt A, et al. J Am Acad Dermatol. 2022 Apr;86(4):827-834.

Guselkumab (IL-23): Efficacy and Safety in Psoriatic Arthritis

ACR20 and ACR50 Response Among PsA Patients With and Without Prior TNFi Experience Treated with GUS Q4W and Q8W (DISCOVER 1)



Continuous Improvement in Key PsA Domains Among Bio-Naïve Patients Treated with GUS Q4W (DISCOVER 2)



- **Pooled safety of four Phase 2-3 clinical trials involving 1508 PsA patients and representing 2125 PY**
  - Rates of AEs were similar between GUS and PBO through week 24, with no increase through year 2 regardless of dose regimen or prior TNFi use
  - Observed lab abnormalities were generally mild and without clinical complications

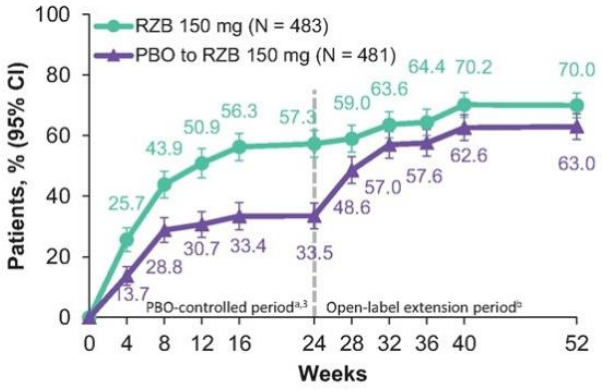
AEs = Adverse Events; GUS = guselkumab; DSS = Dactylitis Severity Score; LEI = Leeds Enthesitis Index; PASI = Psoriasis Area and Severity Index; PBO = placebo; SJC = swollen joint count; TJC = tender joint count; PY = patient years.

Deodhar A, et al. Lancet. 2020 Apr 4;395(10230):1115-1125; Coates LC, et al. POS1017. Presented at EULAR 2022. June 1-4 2022. Copenhagen & Virtual; Rahman P, et al. POS1015. Presented at EULAR 2022. June 1-4 2022. Copenhagen & Virtual.

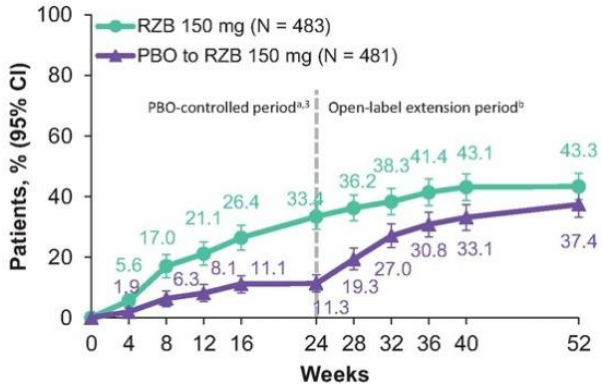
Risankizumab (IL-23): Efficacy in Active Psoriatic Arthritis

52-Week Results of the KEEPsAKE 1 Phase 3 Study: Patients With Inadequate Response or Intolerance to cdDMARDS

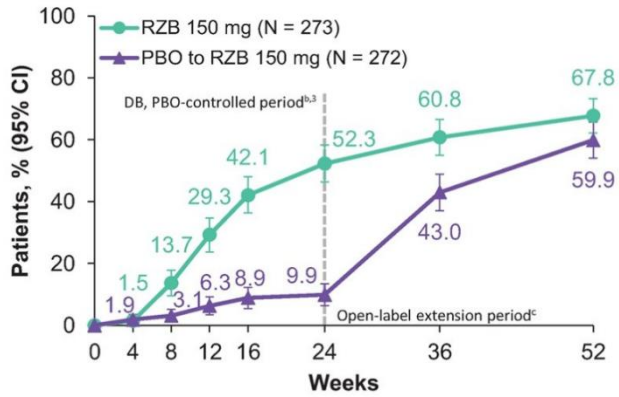
ACR 20



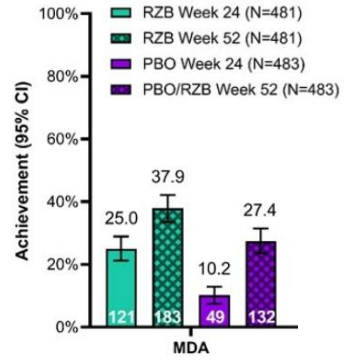
ACR 50



PASI 90

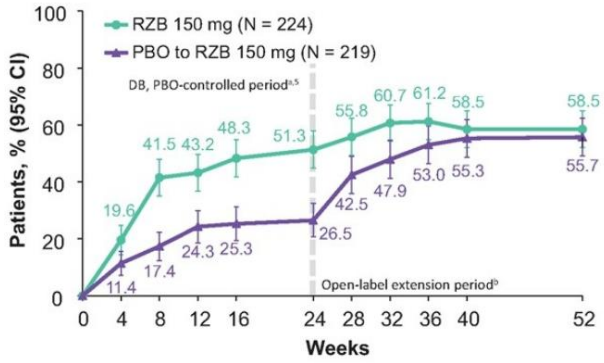


MDA

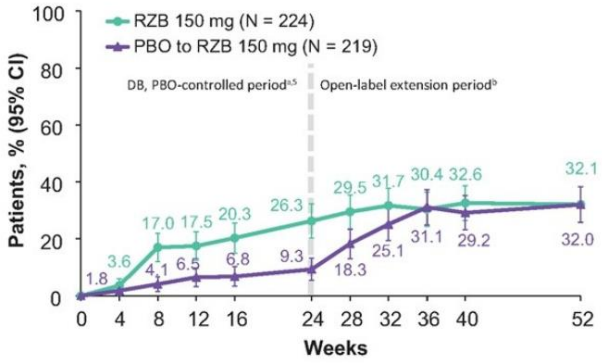


52-Week Results of the KEEPsAKE 2 Phase 3 Study: Patients With Inadequate Response or Intolerance to bDMARDS

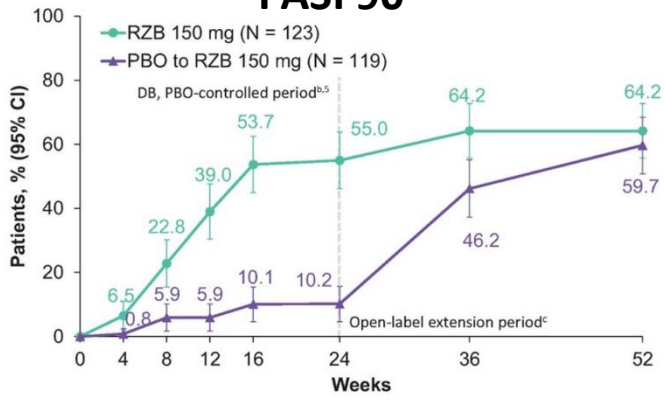
ACR 20



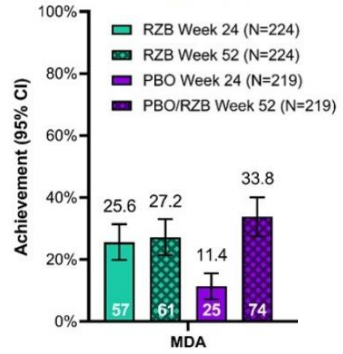
ACR 50



PASI 90



MDA

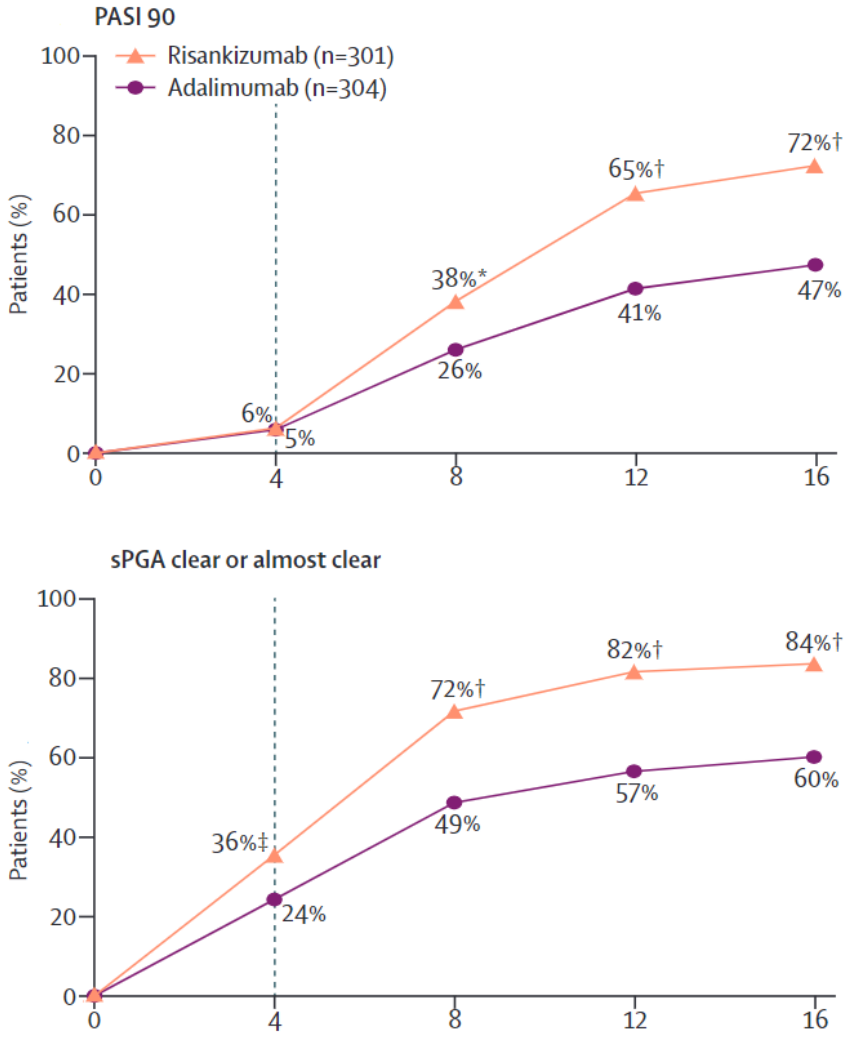


MDA = minimal disease activity; RZB = risankizumab

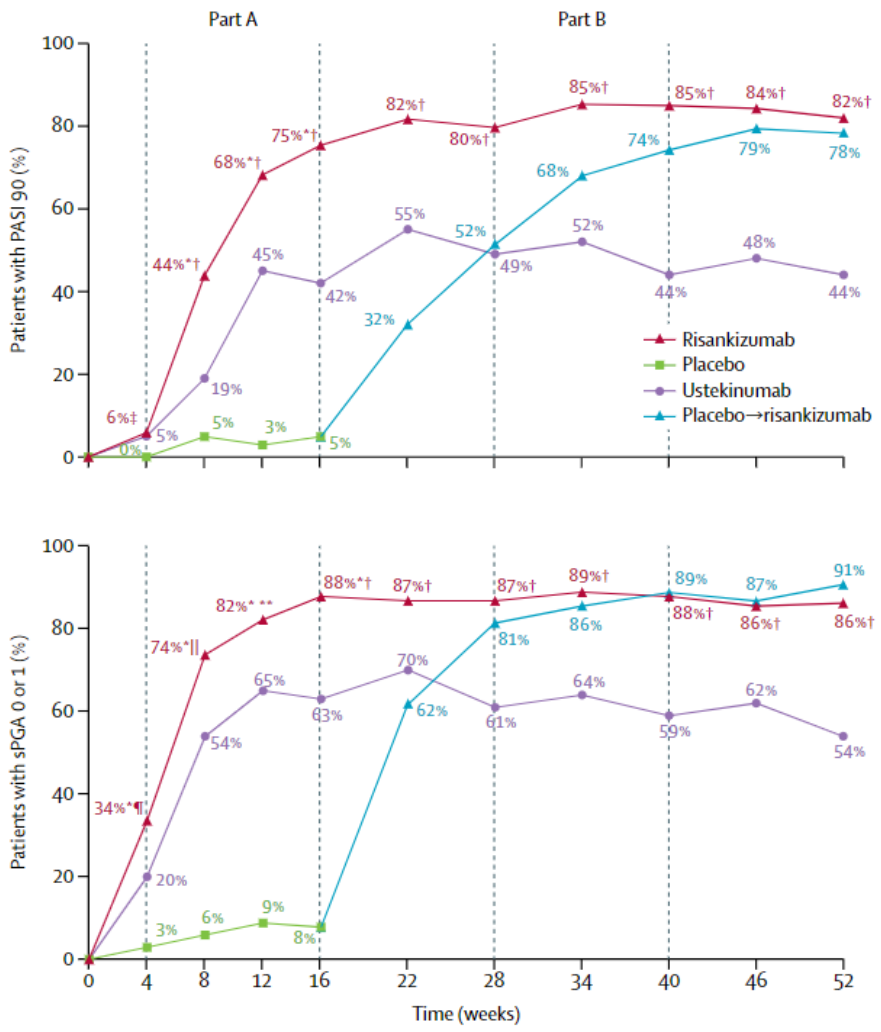
Kristensen LE, et al. POS1024. Presented at EULAR 2022. June 1-4 2022. Copenhagen & Virtual; Ostor A, et al. POS1036. Presented at EULAR 2022. June 1-4 2022. Copenhagen & Virtual; Merola JF, et al. POS1029. Presented at EULAR 2022. June 1-4 2022. Copenhagen & Virtual

Risankizumab (IL-23) vs. Active Comparators: Efficacy in Psoriasis

IMMvent Phase 3 Trial



UltIMMa-1 Phase 3 Trial



PASI = Psoriasis Area and Severity Index; sPGA = static Physician's Global Assessment

Reich K, et al. Lancet. 2019 Aug 17;394(10198):576-586;
Gordon KB, et al. Lancet. 2018 Aug 25;392(10148):650-661.

Risankizumab (IL-23): Pooled Safety in Psoriatic Diseases

Pooled safety data from 17 clinical trials in Psoriasis and 4 in Psoriatic Arthritis

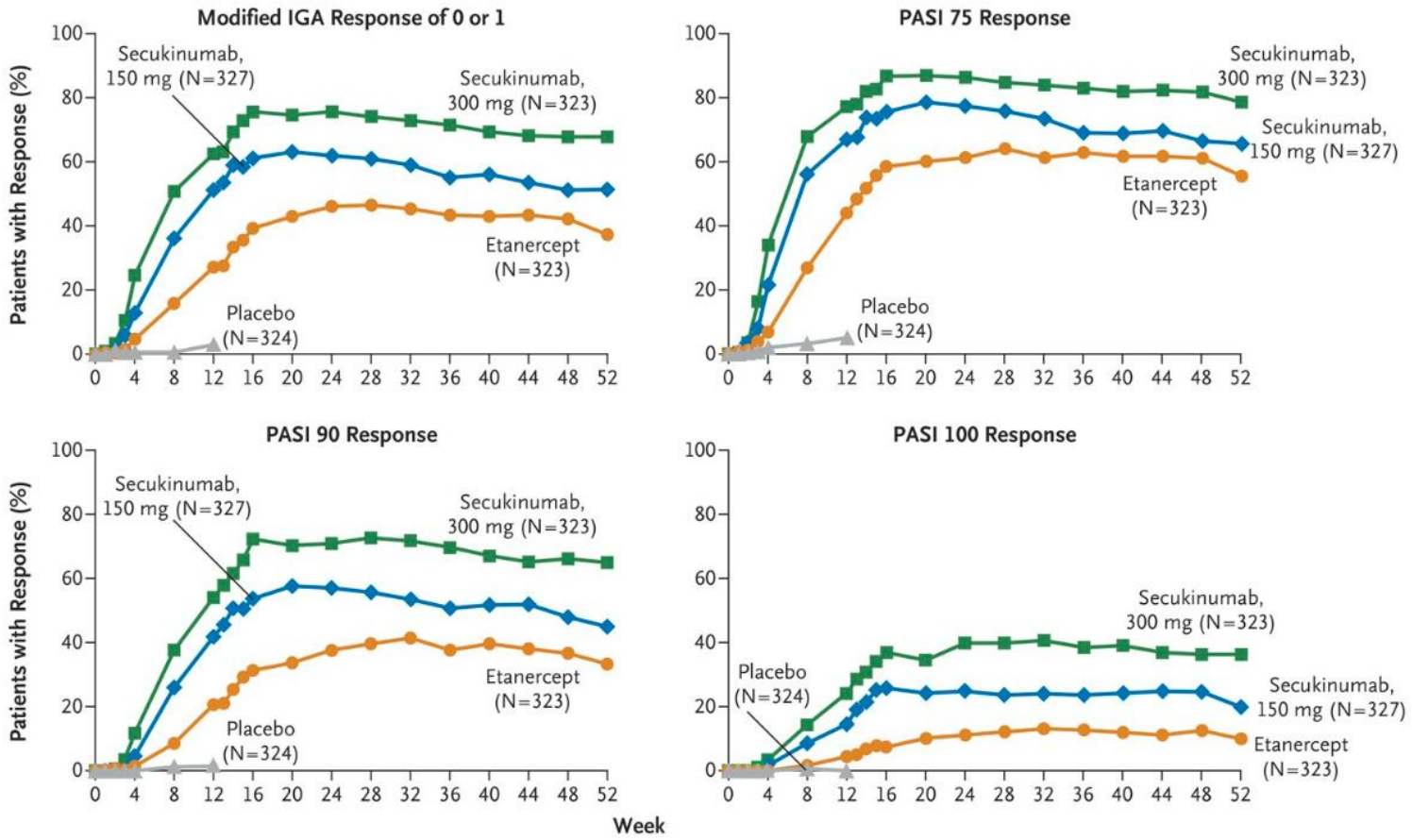
Events per 100PY	Patients with PsO (n=3197, 9982.6 PY)	Patients with PsA (n=1542, 1594.9 PY)
AEs	158.3	160.8
Serious AEs	7.6	8.4
AEs Leading to Discontinuation	1.9	2.3
Most Common Infections		
Nasopharyngitis	14.5	7.9
Upper respiratory infection	7.8	5.6
Serious Infections		
Pneumonia	0.1	0.3
Sepsis	0.1	<0.1
COVID-19	<0.1	0.4
Opportunistic Infections		
Tuberculosis	0	0
Candida	0.5	0.3
Malignancies	1.2	0.8
MACE	0.5	0.4
Injection Site Reactions	3.1	1.6

PY = patient years; MACE = major adverse cardiovascular events.

Gordon KB, et al. POS1023. Presented at EULAR 2022. June 1-4 2022. Copenhagen & Virtual

Secukinumab (IL-17A): Efficacy in Moderate-to-Severe & Hard-to-Treat PsO

FIXTURE Phase 3 Clinical Trial of Secukinumab (300mg or 150mg QW) vs Etanercept (50mg QW)



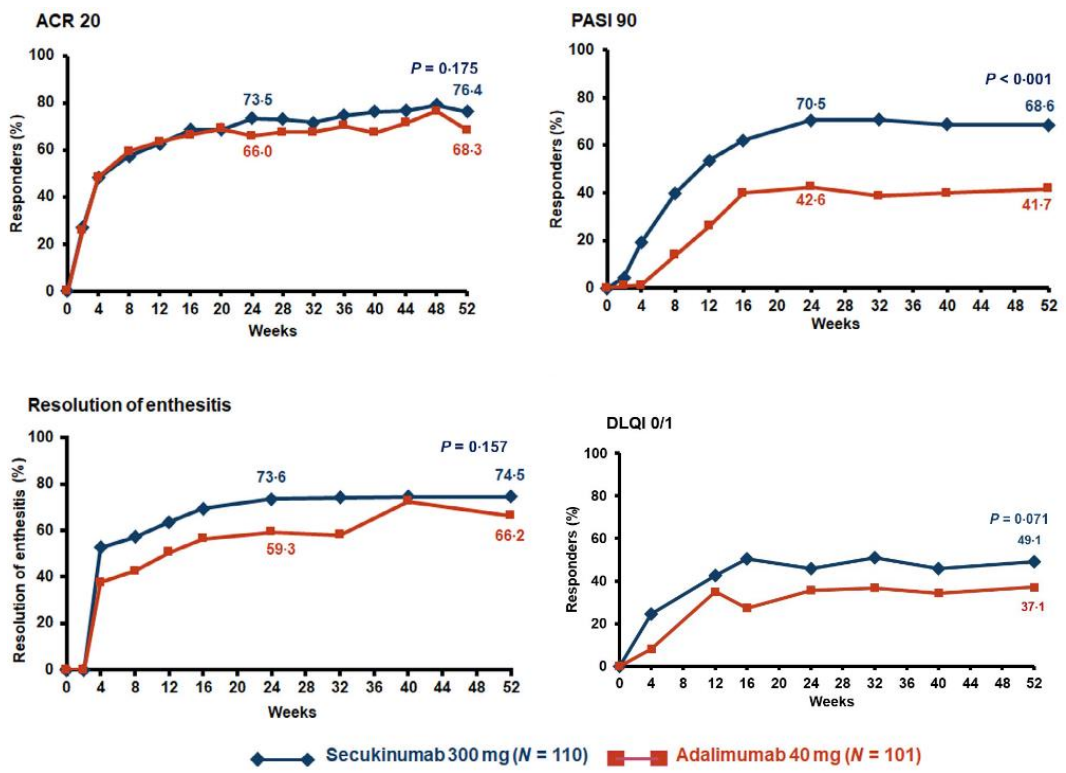
- **TRANSFIGURE Study:**
  - Secukinumab resulted in significant nail psoriasis (NAPSI score) improvements from baseline (60-70%) that were maintained after 2.5 years of treatment
- **GESTURE Study:**
  - About half of secukinumab-treated patients with moderate to severe palmoplantar psoriasis achieved and maintained clear or almost clear palms and soles (ppIGA 0 or 1) after 2.5 years of treatment

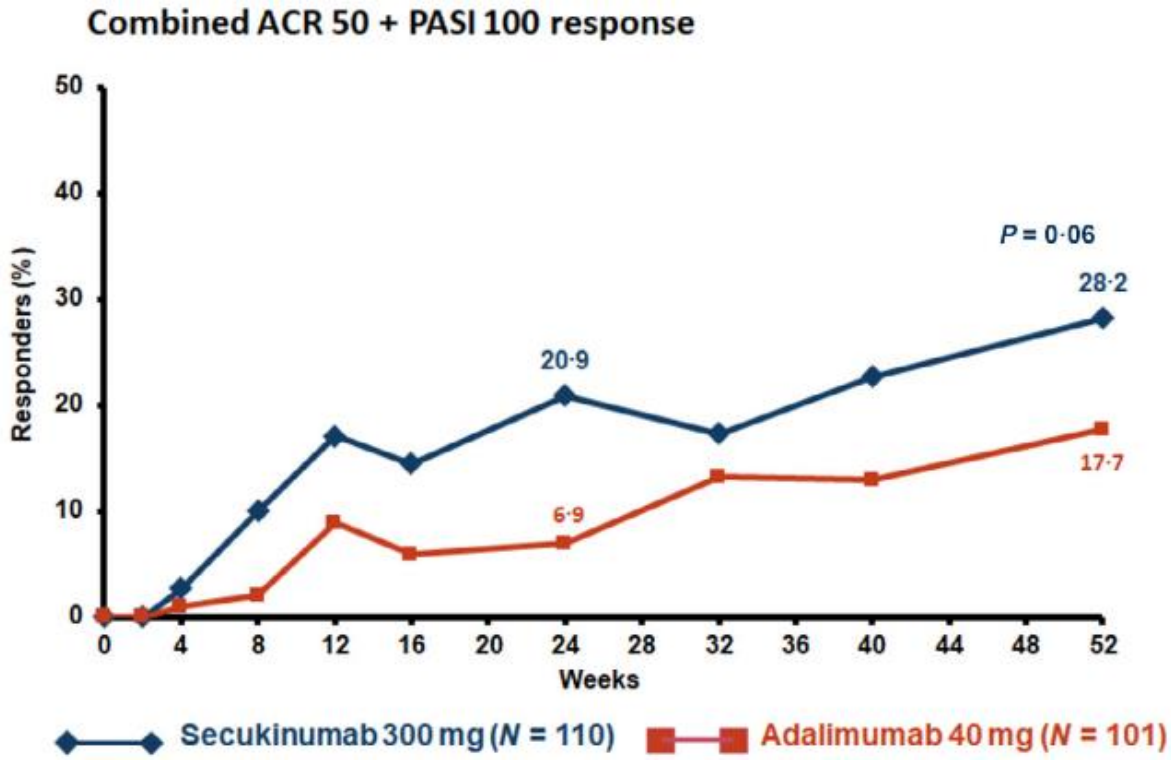
IGA = Investigator's Global Assessment ; NAPSI = Nail Psoriasis Severity Index; PASI = Psoriasis Area and Severity Index; ppIGA = palmoplantar Investigator's Global Assessment.

Langley RG, et al. N Engl J Med. 2014 Jul 24;371(4):326-38; Reich K, et al. Br J Dermatol. 2021 Mar;184(3):425-436; Gottlieb AB, et al. Br J Dermatol. 2020 Apr;182(4):889-899.

Secukinumab vs. Adalimumab: PsA and Concomitant Psoriasis

Post-hoc analysis of EXCEED, a head-to-head study to evaluate secukinumab (300 mg SC QW then Q4W) vs adalimumab (40 mg Q2W) treatment for ≈50 weeks in 853 patients with active PsA and concomitant moderate-to-severe PsO





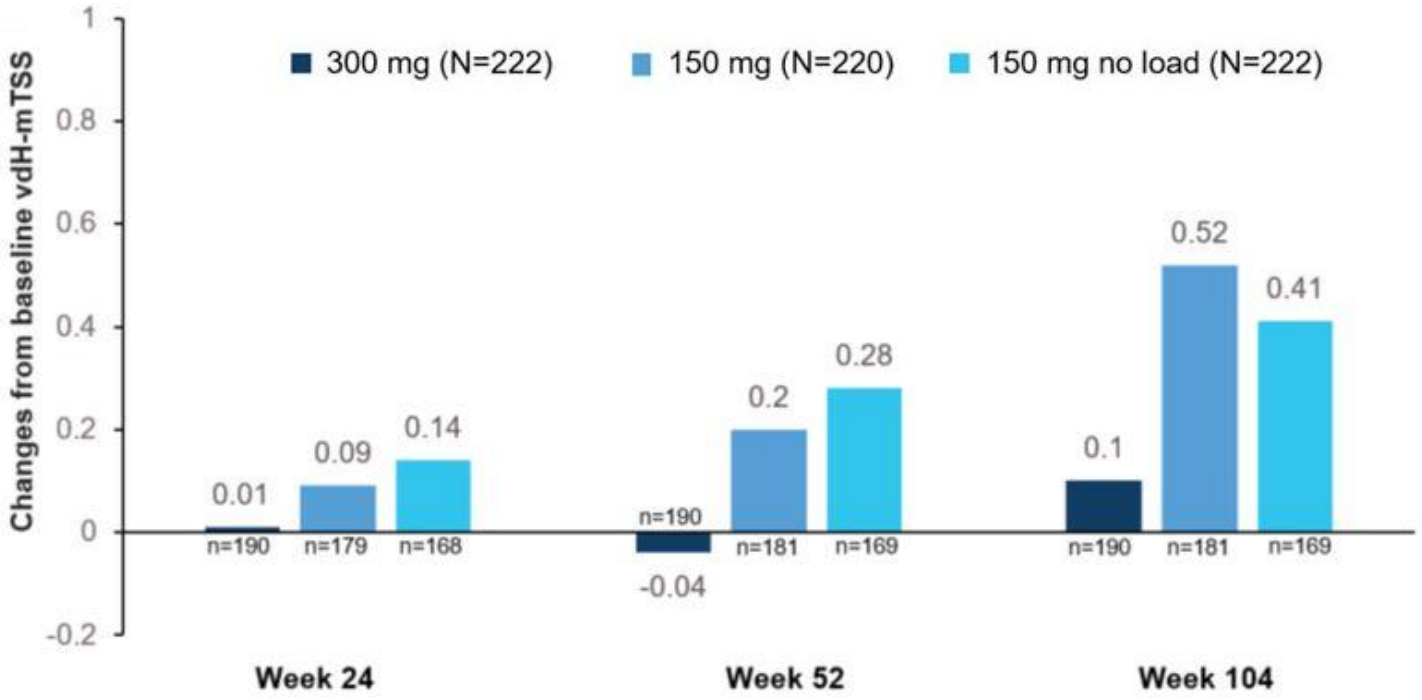
DLQI=Dermatology Life Quality Index

Gottlieb AB, et al. Br J Dermatol. 2021 Dec;185(6):1124-1134.

Secukinumab (IL-17A): Radiographic Progression in Psoriatic Arthritis

FUTURE 5 is a 2-year phase 3 study to evaluate the impact of secukinumab 300 and 150 mg on clinical signs and symptoms and radiographic progression as well as evaluating the short-term benefit of the loading regimen

2-Year Radiographic Progression in the Overall Population



- **Proportion of patients with no radiographic progression at 2-years**
  - 300mg = 89.5%
  - 150mg = 82.3%
  - 150mg no load = 81.1%
- **Subanalysis comparing progression between TNFi-naïve vs TNFi-IR patients**
  - Mean changes from baseline followed a similar trend of low radiographic progression to the overall population
  - Lower rates of progression in TNF-naïve patients vs TNF-IR patients

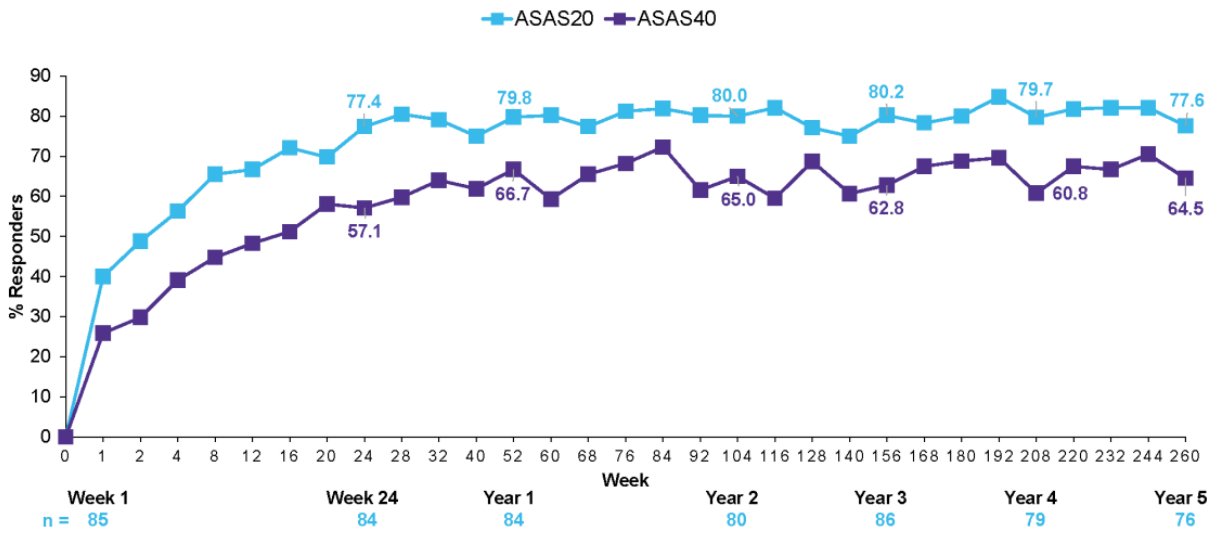
vdH-mTSS = van der Heijde-modified total Sharp score;
TNFi-IR = TNF inadequate responders.

Mease PJ, et al. RMD Open. 2021 Jul;7(2):e001600.

Secukinumab (IL-17A):Efficacy in Ankylosing Spondylitis

5-Year Clinical Efficacy Outcomes of SEC 150 mg

Data from MEASURE 1 study*



- 56.2% of patients originally randomised to secukinumab 75mg required dose escalation to secukinumab 150mg during the study
- Responses were improved in patients whose dose was escalated

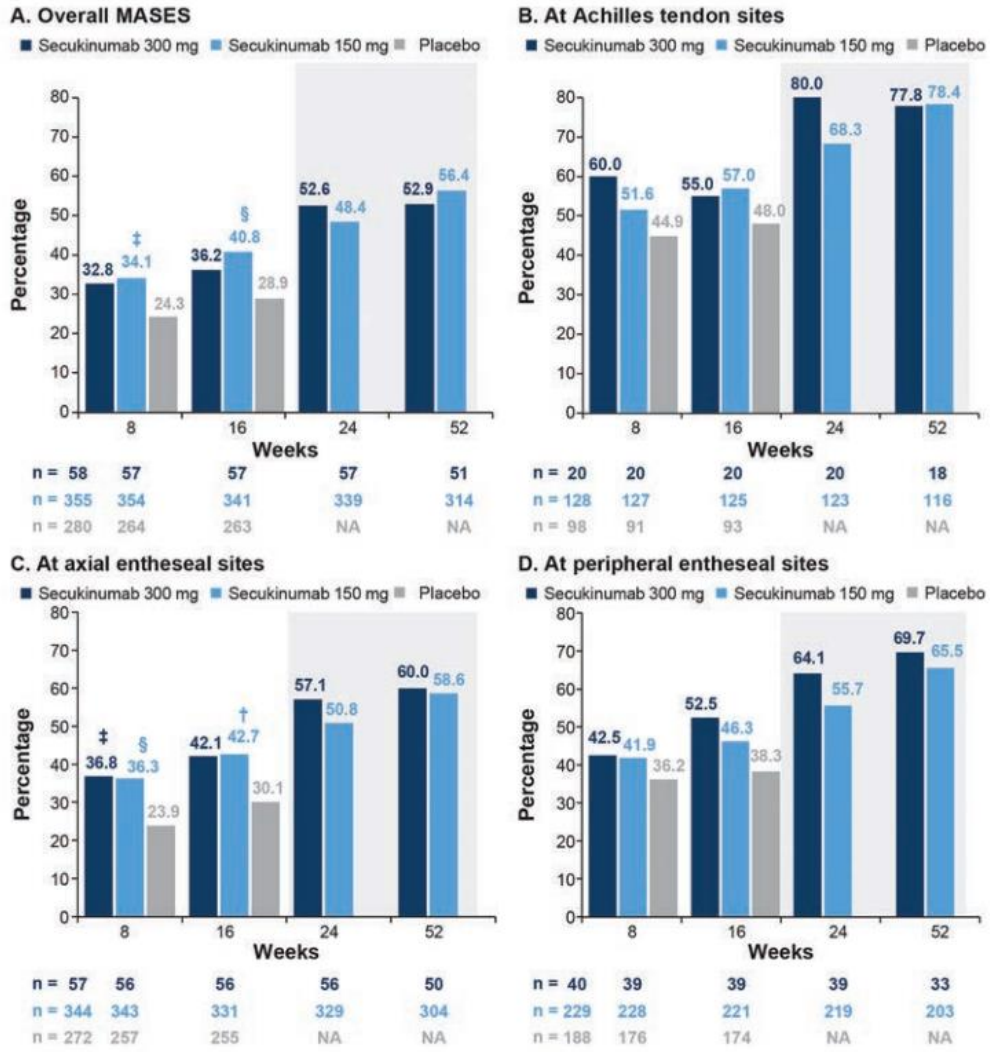
***After the 2-year core trial, patients receiving SC secukinumab 150 or 75 mg were invited to enter a 3-year extension trial. Dose escalation from secukinumab 75 to 150 mg was allowed at or after week 156 based on the clinical judgement of the treating physicians.**

SEC= Secukinumab; MASES = Maastrich Ankylosing Spondylitis Enthesitis Score

Baraliakos X, et al. RMD Open. 2019 Sep 3;5(2):e001005; Schett G, et al. J Rheumatol. 2021 Aug;48(8):1251-1258

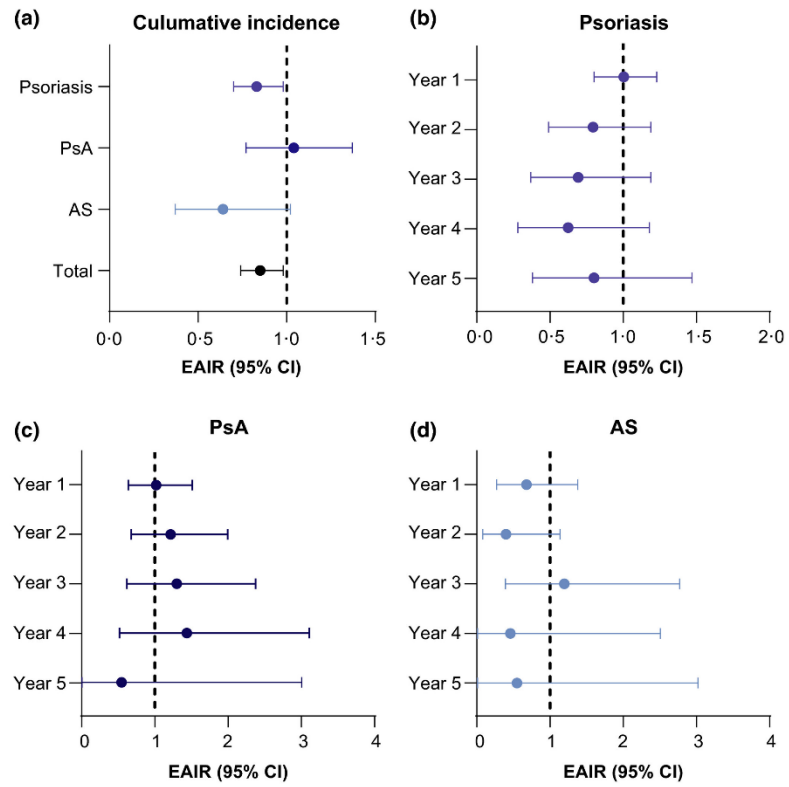
Patients with Complete Resolution of Enthesitis (MASES 0)

Pooled Analysis of MEASURE 1–4 studies



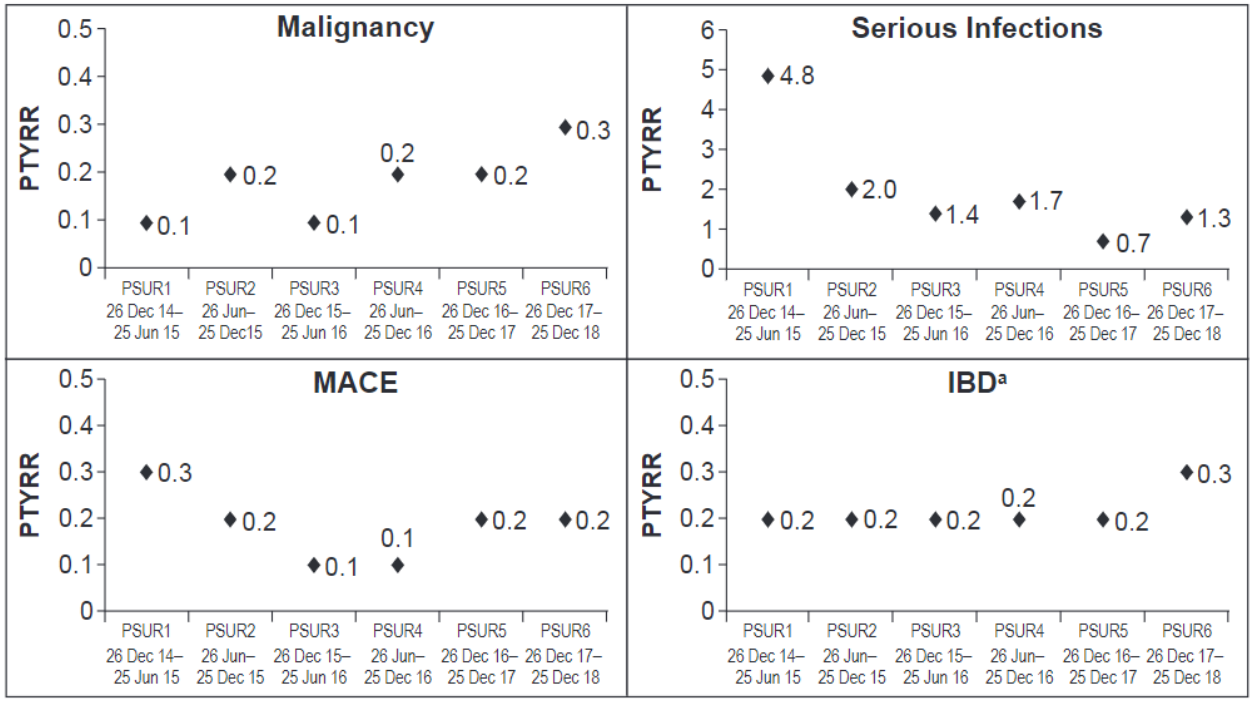
Secukinumab (IL-17A): Pooled Safety Analyses of Clinical Trial and Post-marketing Surveillance Data

Exposure adjusted incidence rates (EAIR) per 100 patient treatment-years of malignancy



23,000 Secukinumab-treated patients, corresponding to 280,000 PTY

Crude incidence (reporting rate) of adverse events with secukinumab across 6 periodic safety update reporting periods



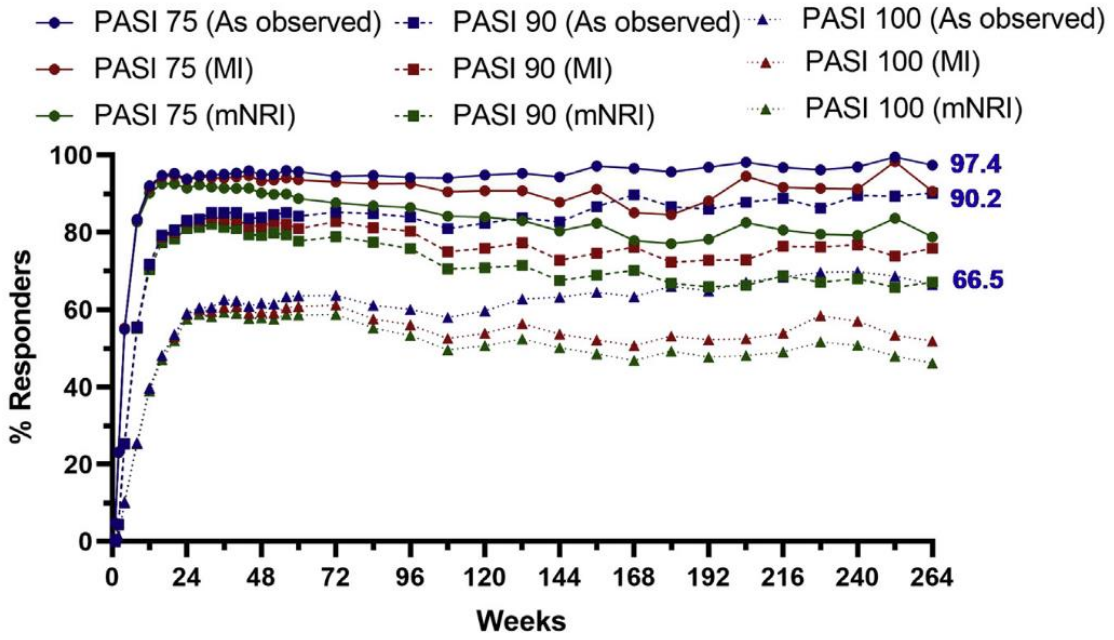
12,637 secukinumab-treated patients, corresponding to 15,063; 5,985; and 3,527 PTY of exposure in psoriasis; psoriatic arthritis; and ankylosing spondylitis patients, respectively.

AS = ankylosing spondylitis; MACE = Major adverse cardiovascular events; IBD = Inflammatory Bowel Disease.

Lebwohl M, et al. Br J Dermatol. 2021 Nov;185(5):935-944; Gottlieb AB, et al. Acta Derm Venereol. 2022 Apr 27;102:adv00698.

Ixekizumab (IL-17A): Long-Term Efficacy and Safety in Patients with Psoriasis

5-Year Efficacy Data from the UNCOVER-3 Phase 3 Clinical Trial Evaluating Patients on IXE 80 mg every 2 weeks/IXE every 4 weeks (n = 385)



Measure	Year 1	Year 5
sPGA of 0/1	87.5%	90.7%
sPGA of 0	63.3%	66.5%
NAPSI of 0	67.8%	77.2%
PSSI of 0	86.6%	87.3%
PASI 100	86.6%	90.2%

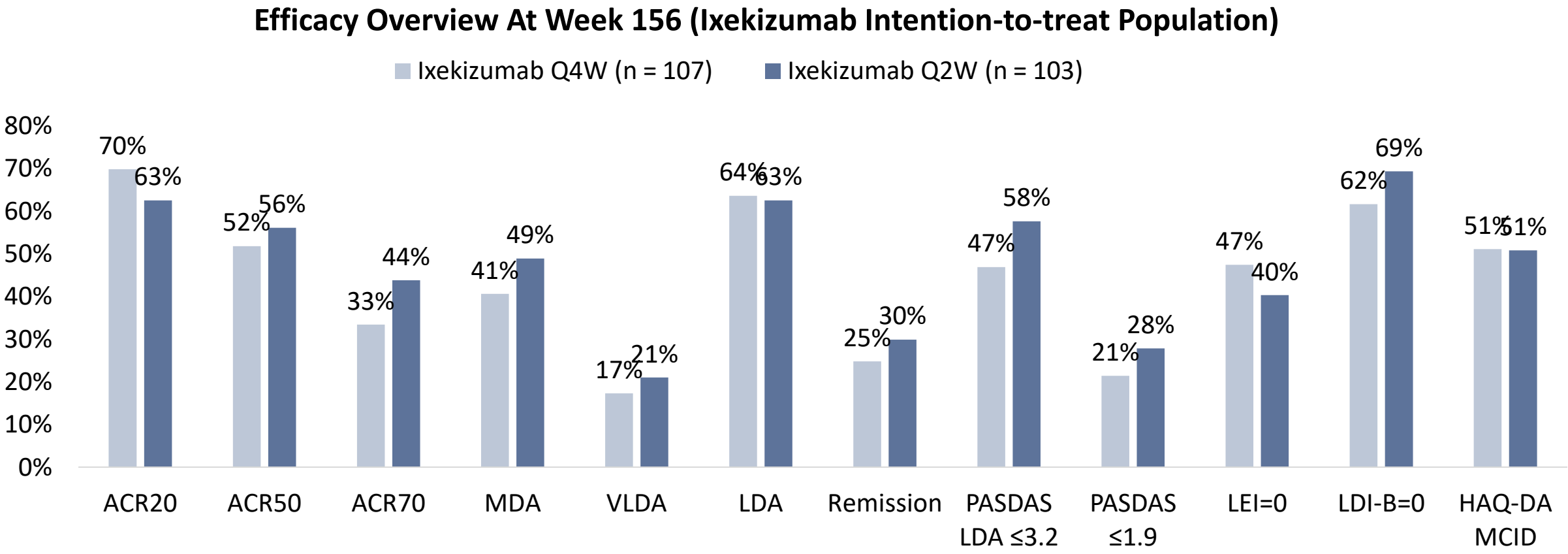
- TEAEs occurred in 323 patients (IR per 100 patient years, 21.6) and Serious TEAEs in 55 patients (IR, 3.7) during the LTE period
- Most frequently reported TEAEs were nasopharyngitis and upper respiratory tract infection, and the most frequent serious TEAEs were infections
- Discontinuations related to study drug TEAE occurred in thirty-three patients(IR, 2.2) over the entire LTE period
- Allergic reactions and hypersensitivities was higher during year 1 (IR, 11) and decreased by year 5 (IR, 3.3)
- Cerebrocardiovascular events were reported by 13 patients (IR, 0.9); IBD events were reported by 3 patients, 2 led to discontinuations
- During the LTE period, 3 (IR, 0.2) deaths were noted; causes of death were hemorrhagic cerebral infarction, complication due to postoperative situation, and death due to unknown cause. In all 3 cases, deaths were not considered to be related to IXE

IXE = ixekizumab; LTE = long-term extensions ; NAPSI = Nail Psoriasis Severity Index; PSSI = Psoriasis Scalp Severity Index; sPGA = static Physician's Global Assessment ;TEAEs = Treatment Emergent Adverse Event.

Blauvelt A, et al. J Am Acad Dermatol. 2021 Aug;85(2):360-368.

Ixekizumab (IL-17A): Efficacy Across Measures of PsA Disease Activity

SPIRIT 1 evaluated ixekizumab treatment of biologic-naïve patients with active psoriatic arthritis

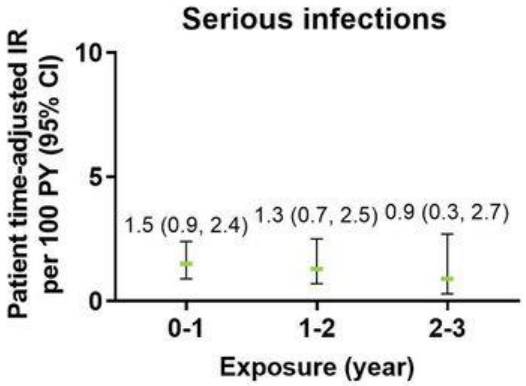


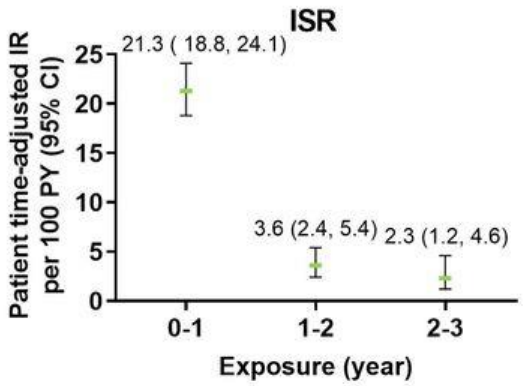
VLDA: very low disease activity; LDA: low disease activity; PASDAS: psoriatic arthritis disease activity score; LEI: Leeds enthesitis index; LDI-B: Leeds dactylitis index-basic; HAQ-DA = Health Assessment Questionnaire Disability Index; MCID = minimal clinically important difference; MDA = minimum disease activity.

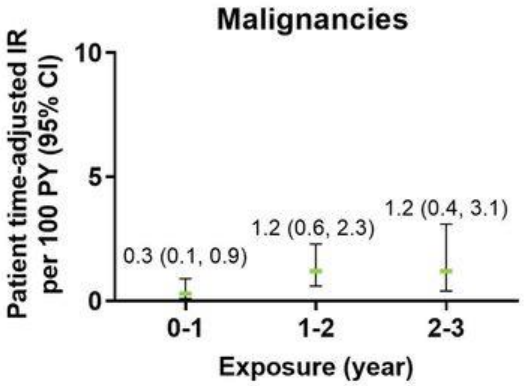
Chandran V,et al. Rheumatology (Oxford). 2020 Oct 1;59(10):2774-2784.

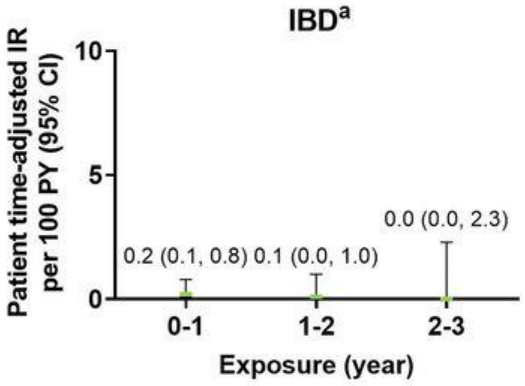
Ixekizumab (IL-17A): Pooled Efficacy in Active PsA

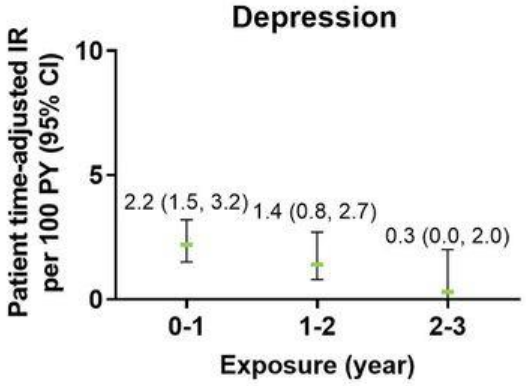
Exposure-adjusted incidence rate/100 patient-years of selected adverse events at successive year intervals from year 0 to year 5 (total 1401 patients with a cumulative ixekizumab exposure of 2247.7 patient-years)

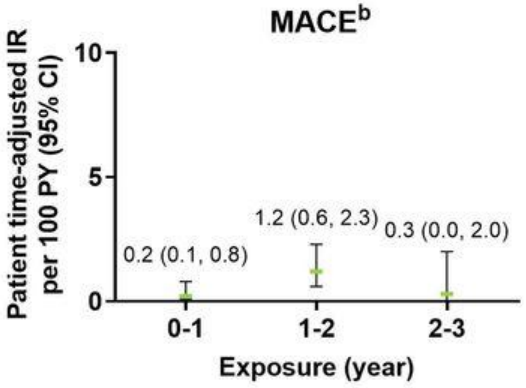












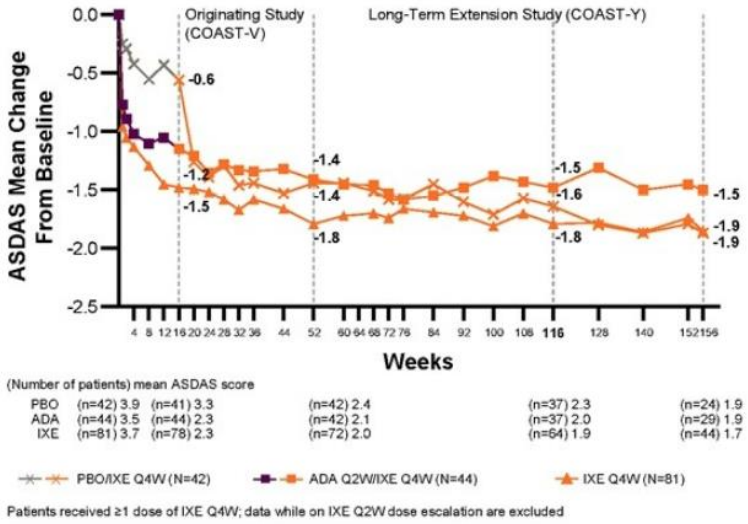
ISR = injection site reactions; IBD = inflammatory bowel disease; MACE = Major adverse cardiovascular events

Deodhar AA, et al. Ann Rheum Dis. 2022 Jul;81(7):944-950.

Ixekizumab (IL-17A): Efficacy in radiographic and non-radiographic AxSpA

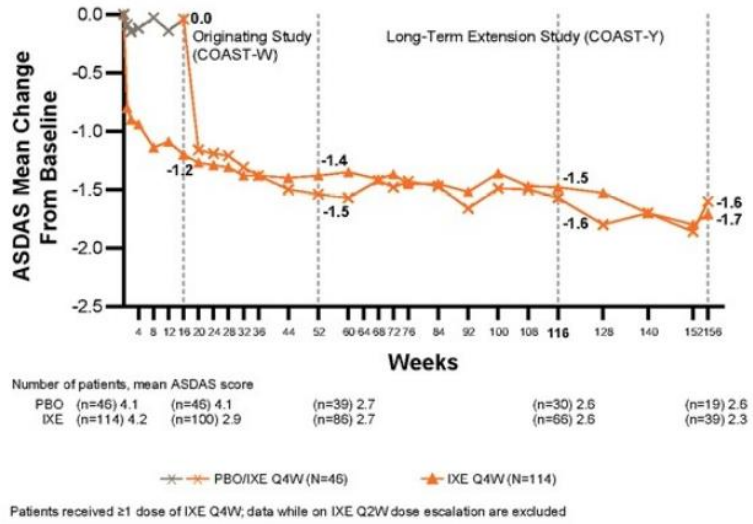
COAST Clinical Trials included patients with AS/r-axSpA and nr-axSpA with or without prior bDMARD exposure. COAST-Y is the long-term extension study with a follow-up period of 3 years.

COAST-V, r-axSpA, bDMARD Naïve



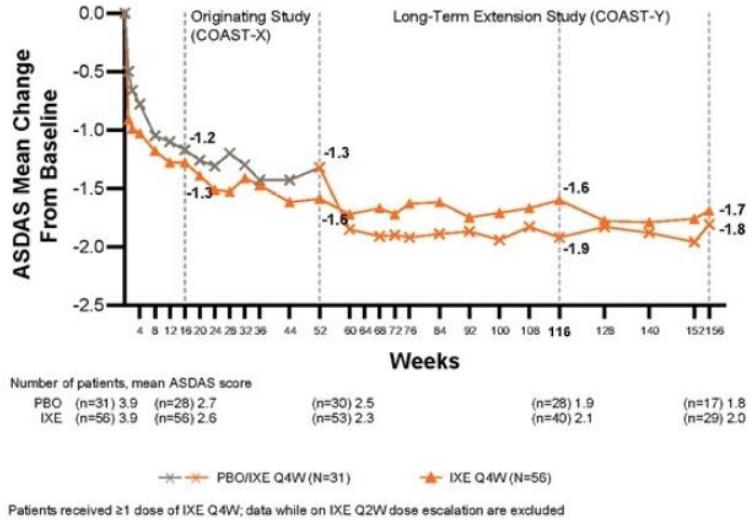
Patients received ≥1 dose of IXE Q4W; data while on IXE Q2W dose escalation are excluded

COAST-W, r-axSpA, TNFi Experienced



Patients received ≥1 dose of IXE Q4W; data while on IXE Q2W dose escalation are excluded

COAST-X, nr-axSpA, bDMARD Naïve



Patients received ≥1 dose of IXE Q4W; data while on IXE Q2W dose escalation are excluded

Pooled Safety Analysis of All Patients Who Received ≥1 IXE Dose

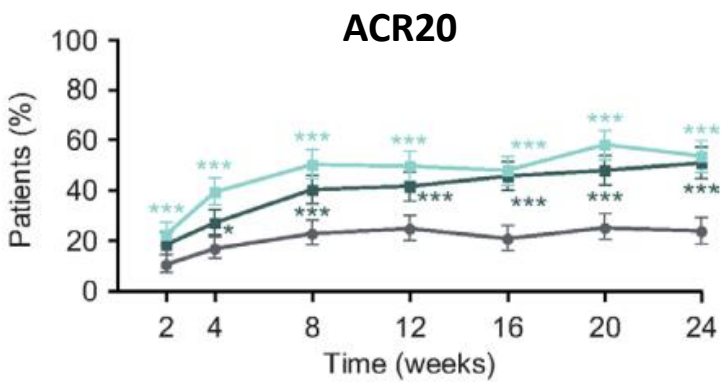
n (%) [EAIR/100 PY]	IXE Q4W (N=454[a]; PY=878.2)	IXE Q2W (N=604[a]; PY=1219.5)	Total IXE (N=932[a]; PY=2097.7)
TEAE overall	380 (83.7) [43.3]	462 (76.5) [37.9]	798 (85.6) [38.0]
TEAE by severity			
Mild	141 (31.1) [16.1]	161 (26.7) [13.2]	276 (29.6) [13.2]
Moderate	198 (43.6) [22.5]	238 (39.4) [19.5]	419 (45.0) [20.0]
Severe	41 (9.0) [4.7]	63 (10.4) [5.2]	103 (11.1) [4.9]
SAE[b]	44 (9.7) [5.0]	57 (9.4) [4.7]	101 (10.8) [4.8]
Discontinuation due to AE	26 (5.7) [3.0]	40 (6.6) [3.3]	66 (7.1) [3.1]
Death[c]	2 (0.4) [0.2]	1 (0.2) [0.1]	3 (0.3) [0.1]

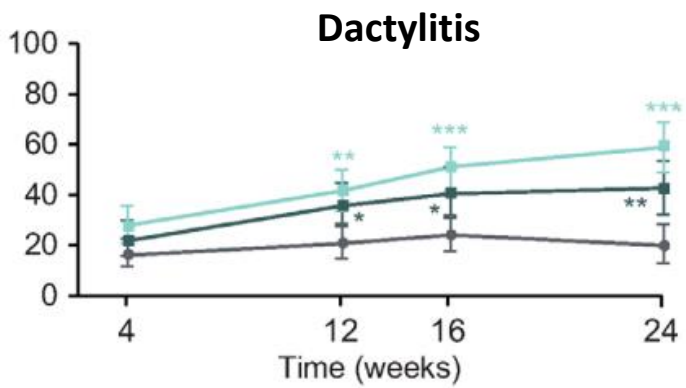
ASDAS = Ankylosing Spondylitis Disease Activity Score; nr-axSpA=Non-radiographic axial spondyloarthritis; r-axSpA = radiographic axial spondyloarthritis.

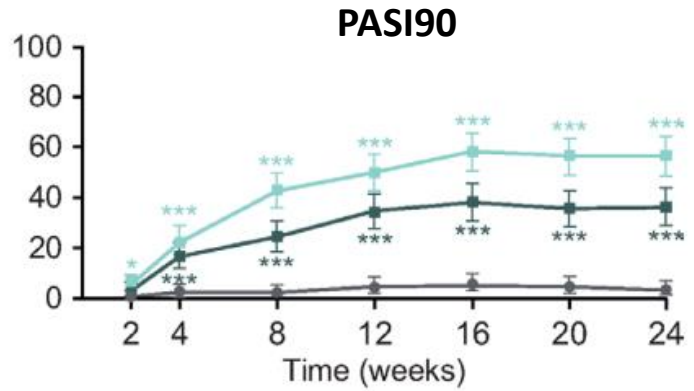
Deodhar A, et al. POS0930 Presented at EULAR 2022. June 1-4 2022. Copenhagen & Virtual;

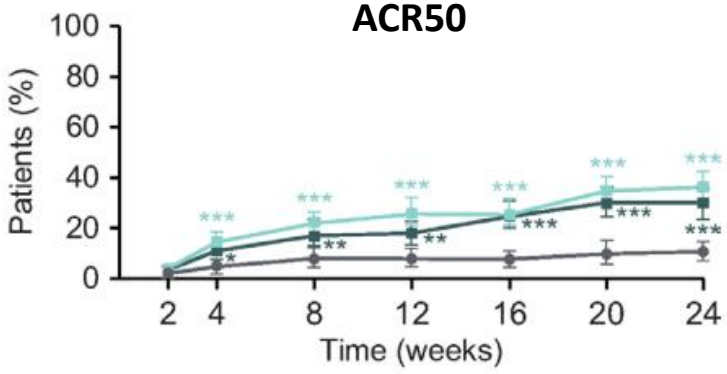
Brodalumab (IL-17AR): Efficacy Across PsA Domains and Measures

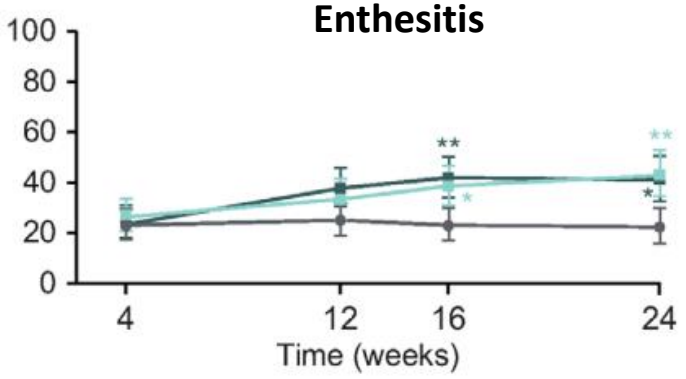
Pooled Efficacy from AMVISION-1 and AMVISION-2 Phase 3 Trials in PsA Patients

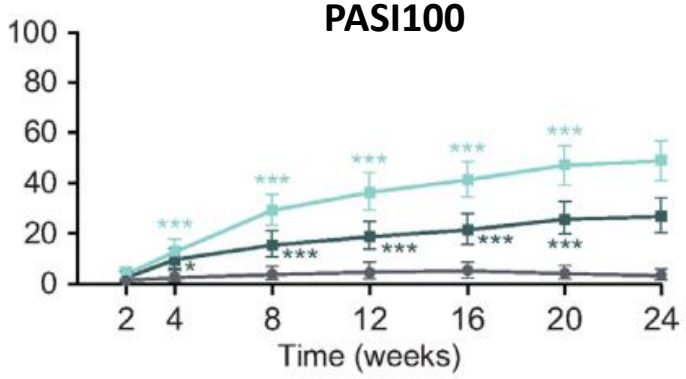












Mease PJ, et al. Ann Rheum Dis. 2021 Feb;80(2):185-193.

Brodalumab (IL-17AR): Safety Considerations

Table 3 Summary of safety: adverse events up to week 16 (safety population, pooled analysis)

AEs, n (%)*	PBO (N=320)	BRO 140 mg Q2W (N=318)	BRO 210 mg Q2W (N=321)
Any AE	174 (54.4)	164 (51.6)	175 (54.5)
AEs causally related to treatment†	62 (19.4)	52 (16.4)	48 (15.0)
SAE	9 (2.8)	6 (1.9)	11 (3.4)
Death	0	0	0
AEs leading to treatment discontinuation	7 (2.2)	3 (0.9)	4 (1.2)
AEs leading to treatment interruption	41 (12.8)	30 (9.4)	38 (11.8)
Selected AEs of interest‡			
Infections and infestations	91 (28.4)	75 (23.6)	96 (29.9)
Crohn's disease	0	0	0
Neutropenia	0	3 (0.9)	3 (0.9)
Suicidal ideation and behaviour	0	1 (0.3)§	0
MACE	2 (0.6)	0	0
Hypersensitivity¶	2 (0.6)	1 (0.3)	7 (2.2)
Malignancy	0	1 (0.3)	1 (0.3)

AE = adverse events; SAE = serious adverse events; PBO = placebo; BRO = brodalumab; MACE = major adverse cardiovascular events

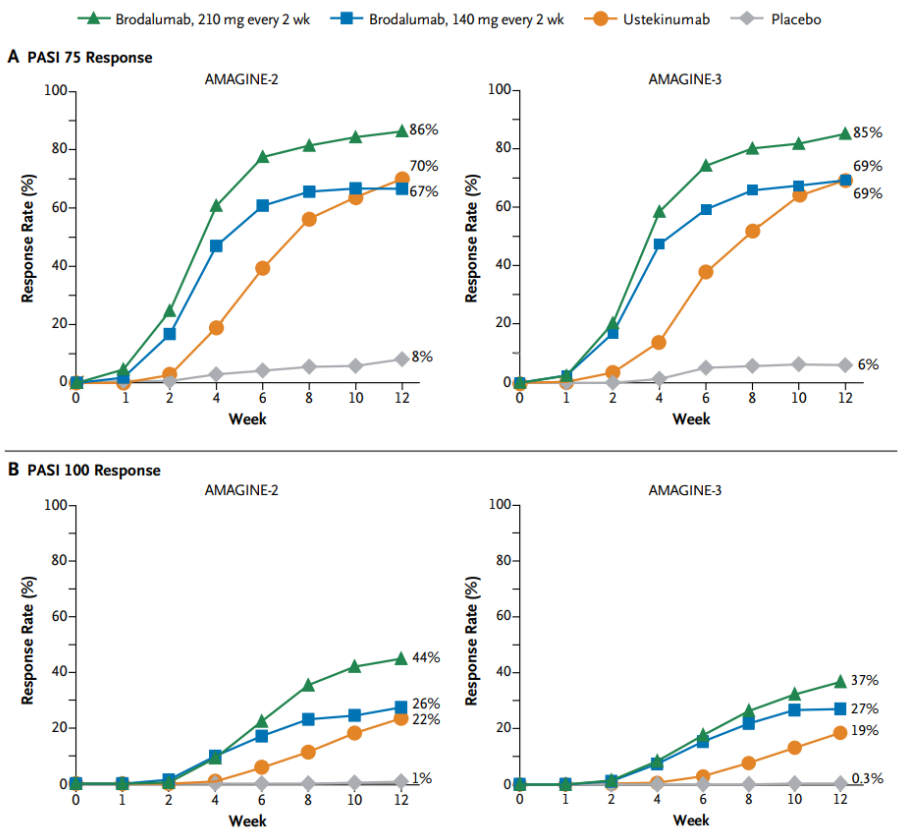
Mease PJ, et al. Ann Rheum Dis. 2021 Feb;80(2):185-193.

Brodalumab vs Ustekinumab in PsO: AMAGINE-2 and AMAGINE-3 trials

AMAGINE-2 and AMAGINE-3 trials were designed to compare the efficacy and safety of brodalumab vs ustekinumab in patients with moderate-to-severe plaque psoriasis

Table 1. Demographics and Baseline Clinical Characteristics of the Patients.*

Characteristic	AMAGINE-2 (N=1831)	AMAGINE-3 (N=1881)
Age — yr	45±13	45±13
Male sex — no. (%)	1258 (69)	1288 (68)
White race — no. (%)†	1652 (90)	1708 (91)
Weight — kg	91±23	89±22
Body-mass index‡	30.6±7.2	30.1±6.9
Duration of psoriasis — yr	19±12	18±12
Psoriatic arthritis — no. (%)	340 (19)	384 (20)
Body-surface area involved — %	27±17	28±18
PASI score§	20.3±8.2	20.2±8.4
sPGA score — no. (%)¶		
3	994 (54)	1169 (62)
4	723 (39)	634 (34)
5	114 (6)	78 (4)
PSI score‖	18.8±6.9	18.5±7.0
Previous systemic treatment or phototherapy — no. (%)	1395 (76)	1287 (68)
Previous biologic therapy — no. (%)	530 (29)	468 (25)



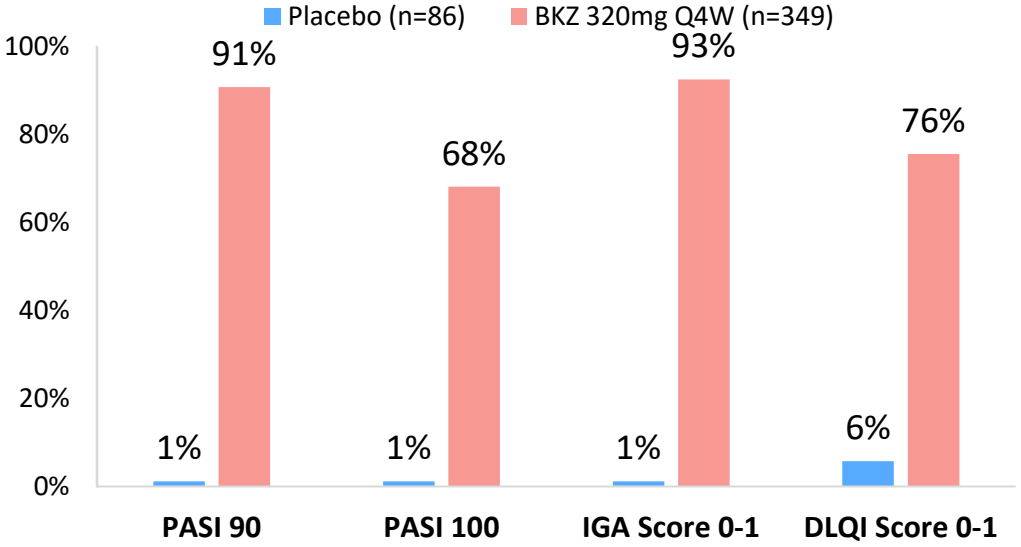
PASI = Psoriasis Area Severity Index ; PSI= Psoriasis Symptom Inventory ;
sPGA = static Physician's Global Assessment.

Lebwohl M, et al. N Engl J Med. 2015 Oct;373(14):1318-28.

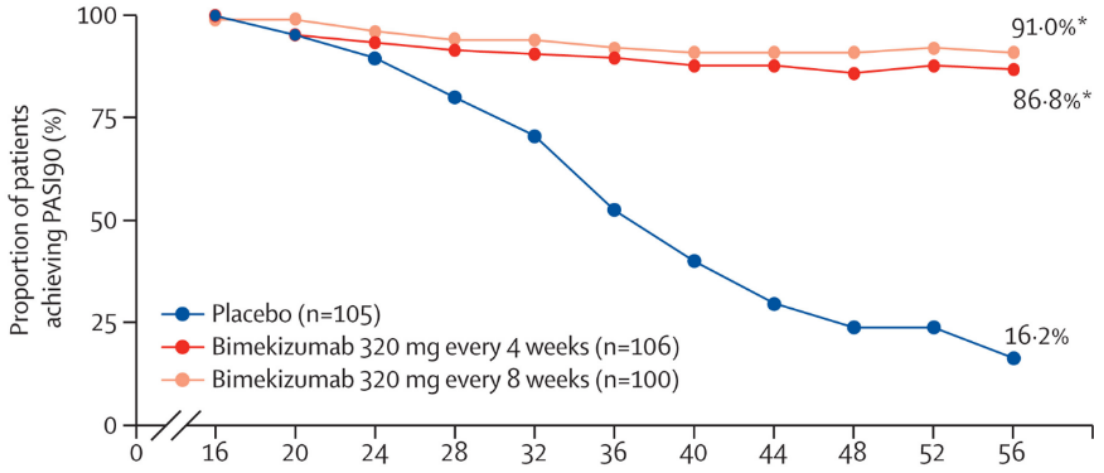
Bimekizumab (IL-17A & IL-17F): Efficacy in Psoriasis

BE READY was a phase 3 study comparing two maintenance dosing schedules (Q4W or Q8W) of bimekizumab through 56 weeks in adult patients with moderate to severe PsO with a withdrawal period after 16 weeks*

Proportion of Patients Achieving Endpoint at Week 16



Proportion of Patients Achieving PASI 90 at Week 56 (Over the Randomized Withdrawal Period*)



- **Safety for initial 16-week treatment period:** 61% of BKZ Q4W patients and 41% of placebo patients had treatment-related AEs; 2% of patients in each arm reported serious AE. Only 3 patients in the BKZ arm discontinued due to treatment-emergent AEs.
- **Safety for the randomized withdrawal period:** comparable rates of AEs and serious AEs were reported across the BKZ Q4W, BKZ Q8W, and placebo arms; discontinuations remained low.
- **Most common AEs:** Nasopharyngitis, oral candidiasis, and URTIs.

AE = adverse events; BKZ = bimekizumab; DLQI=Dermatology Life Quality Index; IGA=Investigator's Global Assessment; URTI = Upper respiratory tract infection

*** At week 16, patients with 90% or greater improvement from baseline in PASI (PASI90) response were re-allocated for treatment through to weeks 16–56.**

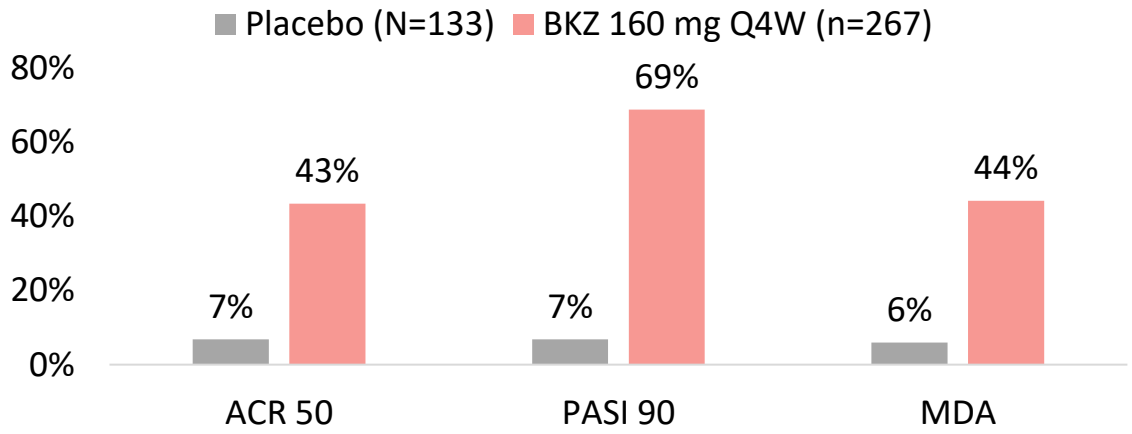
Gordon KB, et al. Lancet. 2021 Feb 6;397(10273):475-486.

Bimekizumab (IL-17A & IL-17F): Efficacy in Psoriatic Arthritis

BE COMPLETE was a phase 3 study evaluating bimekizumab in patients with PsA with inadequate response or intolerance to TNFi for up to Week 16

- **Key Demographic Statistics**
  - PsA duration: PBO 9.2 years, BKZ 9.6 years
  - Concomitant MTX: PBO 38%, BKZ 45%
  - Prior TNF exposure
    - Inadequate response to 1 TNFi: PBO 77%, BKZ 76%
    - Inadequate response to 2 TNFi: PBO 11%, BKZ 11%
    - Intolerance to TNFi: PBO 11%, BKZ 13%
- **Summary of Safety**
  - Any TEAE: PBO 33%, BKZ 40%
  - Serious TEAE: PBO 0%, BKZ 2%
  - Discontinuation due to TEAE: PBO 0%, BKZ 0.7%
  - Drug-related TEAE: PBO 3%, BKZ 13%
  - Severe TEAE: PBO 0%, BKZ 2%
  - Safety profile consistent with prior studies

Efficacy Measures at Week 16



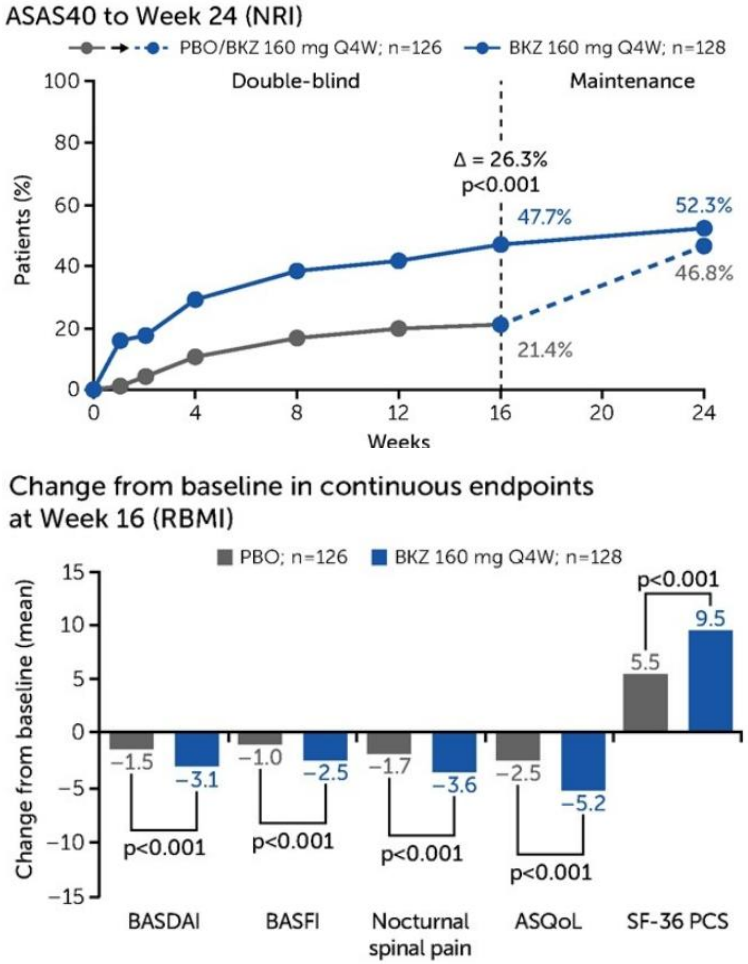
Measure (Change From Baseline)	Placebo (N=133)	BKZ 160mg Q4W (N=267)
HAQ-DI	-0.07	-0.38
SF-36 PCS	1.4	7.3
TJC	-2.4	-10.9
SJC	-2.0	-7.0

BKZ = bimekizumab; HAQ-DI = Health Assessment Questionnaire disability index; PBO = placebo; SF-36 PCS = Short Form Physical Component Score; TJC = Tender Joint Count; SJC = Swollen Joint Count; TEAE: treatment emergent adverse event

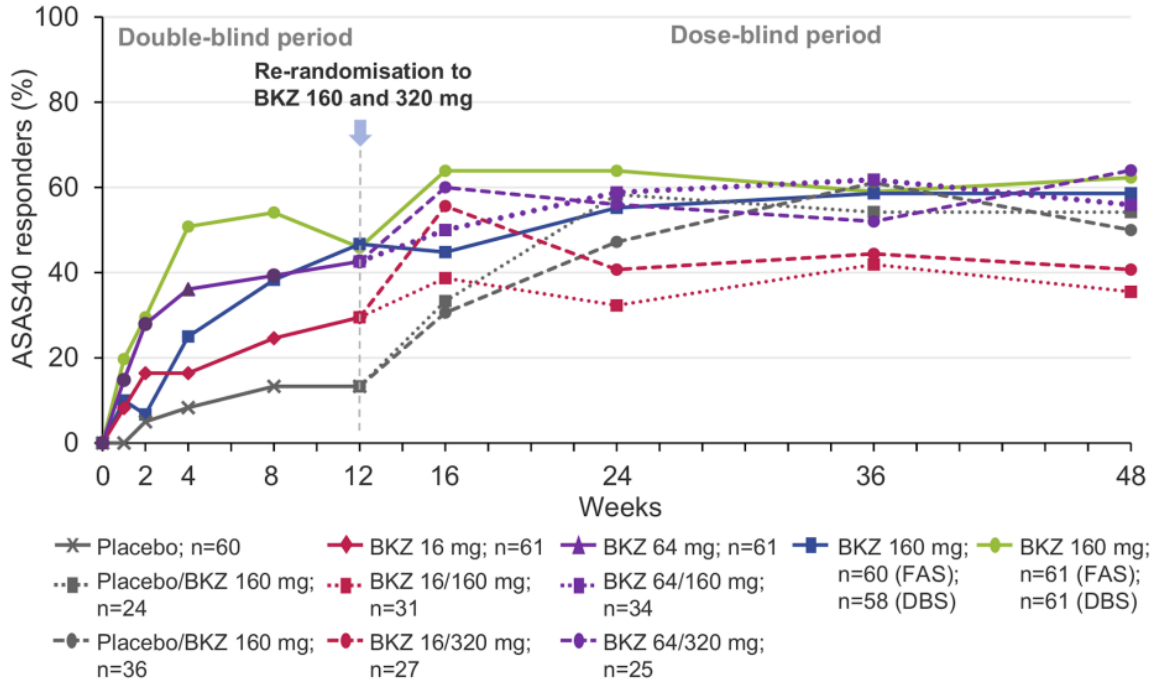
Mease PJ, et al. Rheumatology (Oxford). 2022 Jul 5:keac353.

Bimekizumab (IL-17A & IL-17F): Efficacy in nr-AxSpA and AS

BE MOBILE Phase 3 Study in nr-AxSpA (24 Weeks)



BE AGILE Phase 2B Study in Active AS (48 Weeks)



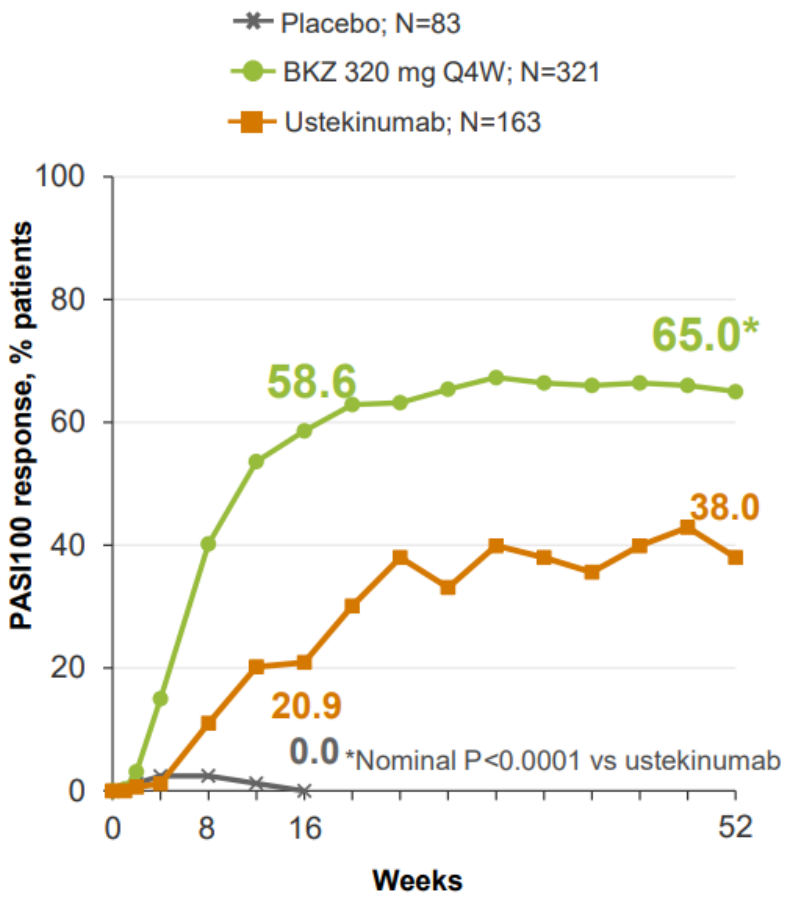
Safety profile in patients with active AS was as expected given previous studies of bimekizumab in patients with PsO or PsA

AS = nkylosing spondylitis; ASAS40 = Assessment of Spondyloarthritis International Society; ASQoL = AS Quality of Life; BASDAI = Bath Ankylosing Spondylitis Disease Activity Index; BASFI = Bath Ankylosing Spondylitis Functional Index; NRI=non-responder imputation; nr-AxSpA = Non-radiographic axial spondyloarthritis; SF-36 PCS = Short Form Physical Component Score.

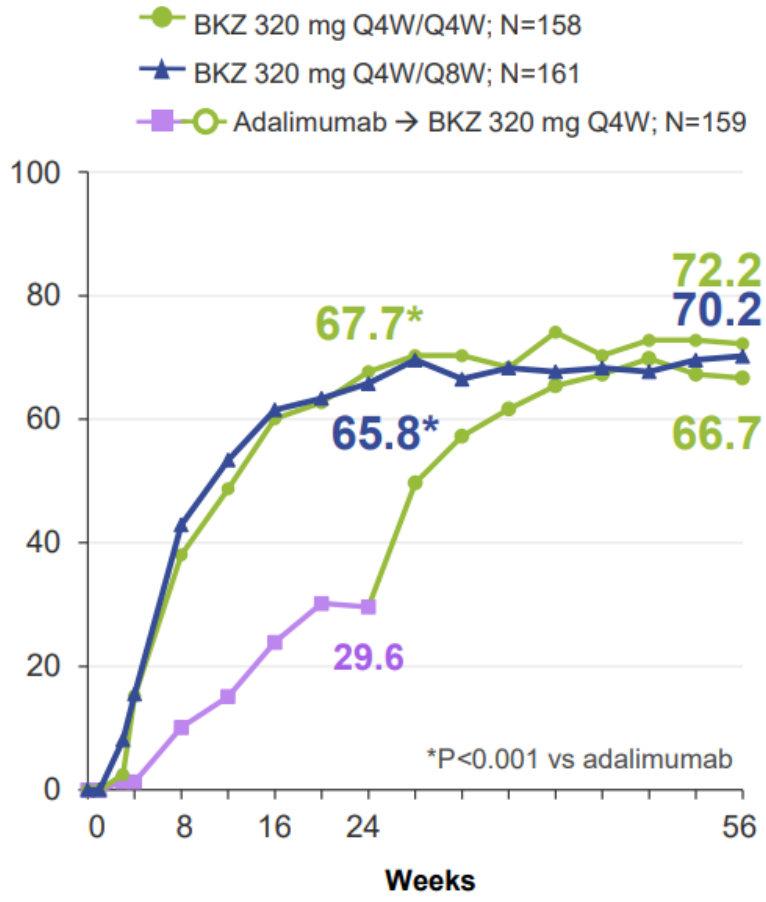
Deodhar A, et al. POS0939 Presented at EULAR 2022. June 1-4 2022. Copenhagen & Virtual; van der Heijde D, et al. Ann Rheum Dis. 2020 May;79(5):595-604.

Bimekizumab vs Active Comparators: Efficacy in PsO at ≈1 Year

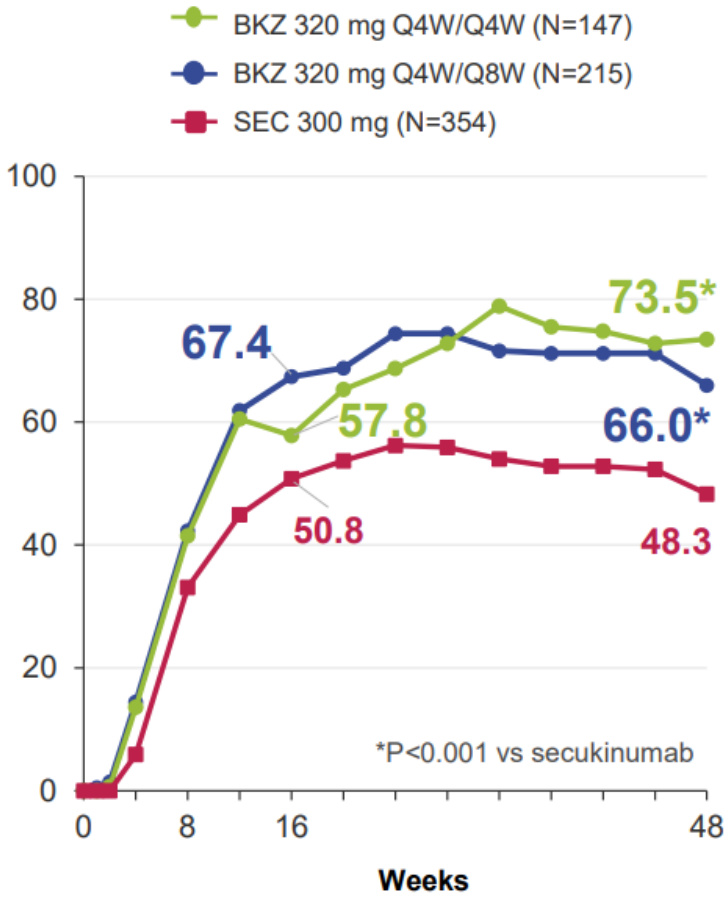
BE VIVID Phase 3 Study



BE SURE Phase 3 Study



BE RADIANT Phase 3 Study

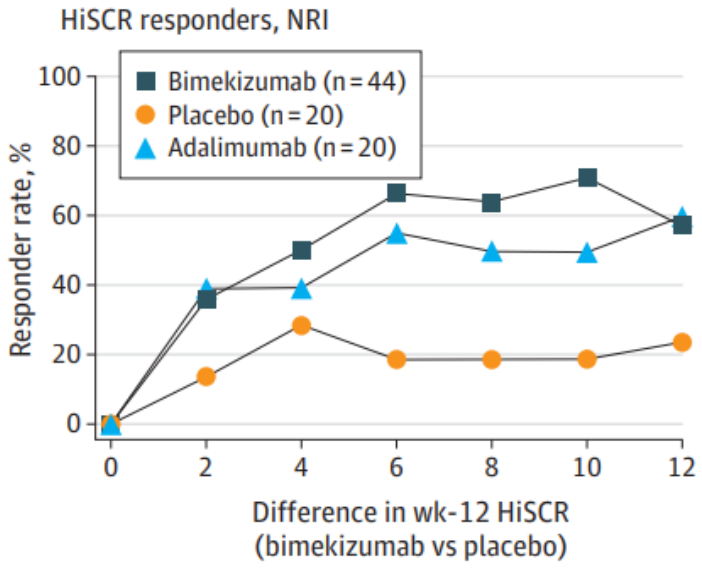


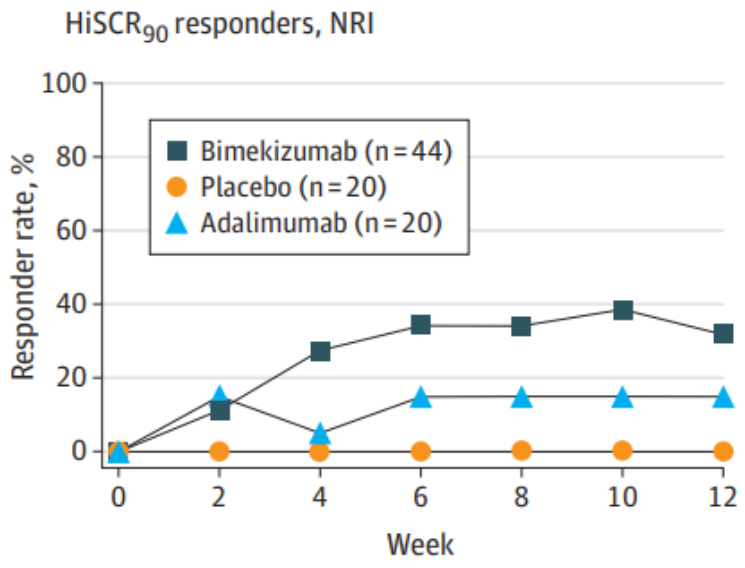
BKZ = bimekizumab; SEC = secukinumab

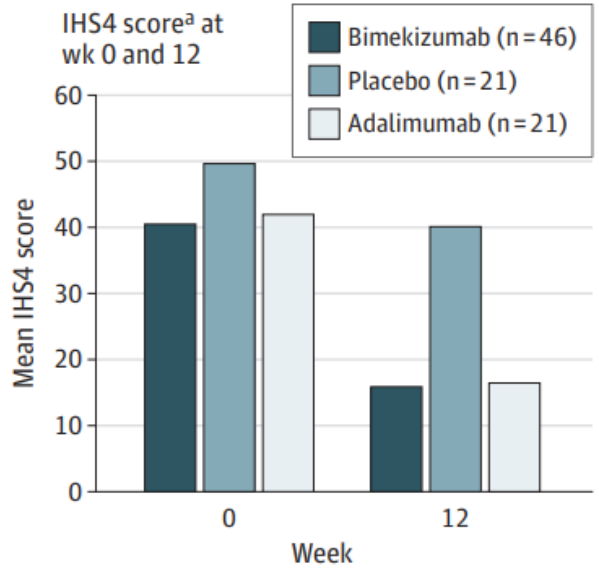
Reich K, et a. Lancet. 2021 Feb 6;397(10273):487-498; Warren RB, et al. N Engl J Med. 2021 Jul 8;385(2):130-141; Reich K, et al. N Engl J Med. 2021 Jul 8;385(2):142-152.

Bimekizumab vs Adalimumab: Efficacy in Hidradenitis Suppurativa (HS)

Phase 2 trial to compare the efficacy and safety of bimekizumab (320mg Q2W) vs adalimumab (40mg QW) in patients with moderate-to-severe with moderate to severe HS







HiSCR: 50% or 90% reduction from baseline in the total AN count, with no increase from baseline in abscess or draining fistula (tunnel) count at week 12.

IHS4: disease severity score based on number of inflammatory nodules, abscesses, and draining fistulae

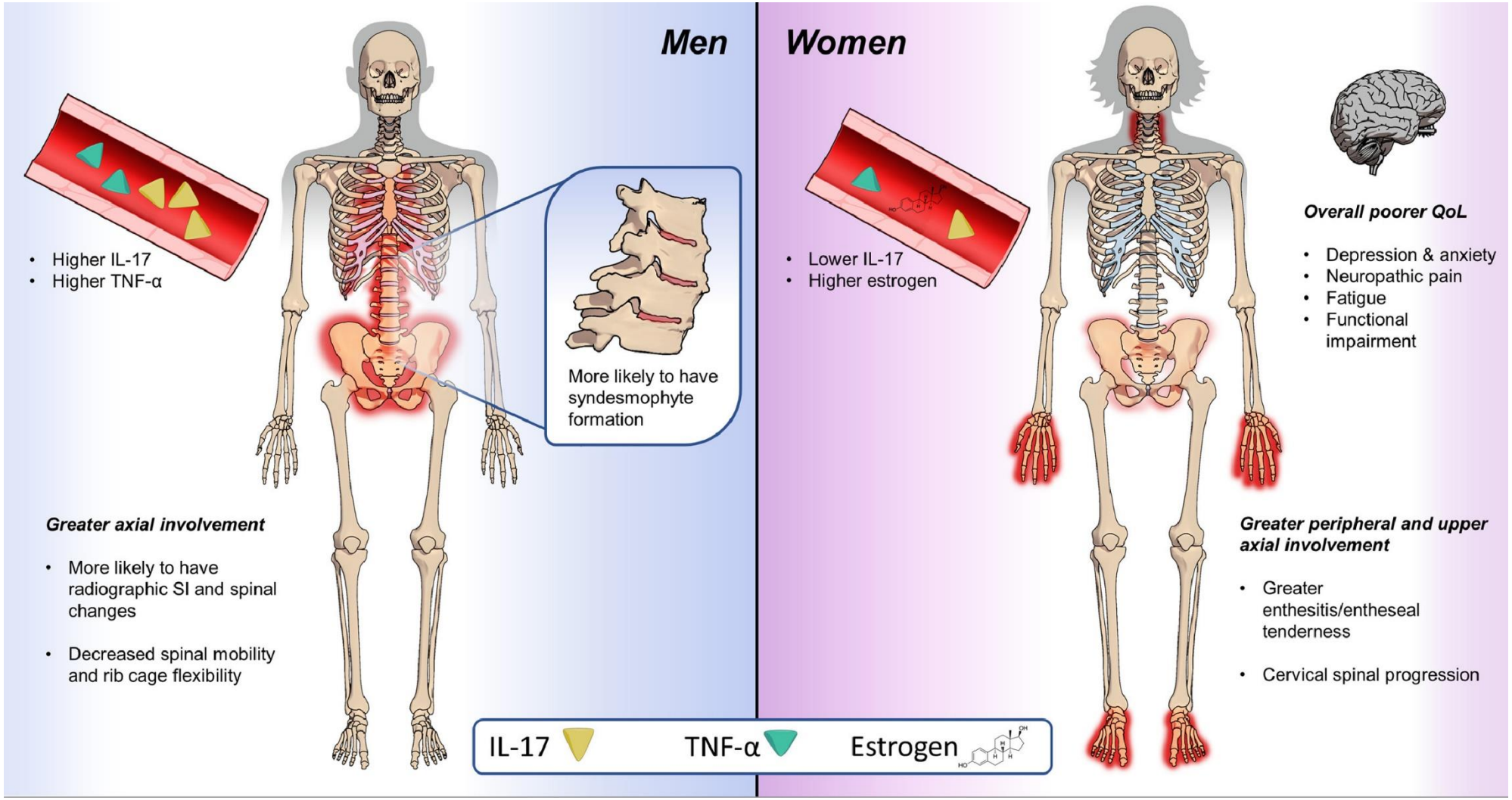
- Incidence of TEAEs and serious TEAEs was similar across treatment arms (bimekizumab, 70%; placebo, 62%; and adalimumab, 71%)
- 1 participant (in the bimekizumab group) discontinued study participation because of a TEAE (worsening HS)
- Safety profile consistent with prior studies, no new or unexpected safety findings

AN count = abscess and inflammatory nodule count; HiSCR = Hidradenitis Suppurativa Clinical Response; IHS4 International Hidradenitis Suppurativa Severity Score;NRI=non-responder imputation;

Glatt S, et al. JAMA Dermatol. 2021 Nov 1;157(11):1279-1288. doi:

Differences in Efficacy and Safety Observed Among Patient Populations

Differences in AS Presentation Between Men and Women



Wright GC, et al. Semin Arthritis Rheum. 2020 Aug;50(4):687-694.

Disease Burden and Activity Between Men and Female with PsA

Post-hoc analysis of EXCEED phase 3 trial that evaluated efficacy and safety of secukinumab versus adalimumab as first-line monotherapy in biologic-naïve patients with PsA

Baseline Demographics and Clinical Characteristics

Variable, mean ± SD unless specified otherwise	Female		Male	
	SEC 300 mg (N = 218)	ADA 40 mg (N = 198)	SEC 300 mg (N = 208)	ADA 40 mg (N = 229)
Age	48.40 ± 11.91	51.30 ± 11.97	48.5 ± 12.88	47.9 ± 12.65
BMI (kg/m^2)	29.09 ± 6.55	29.07 ± 5.97	28.39 ± 5.41	28.73 ± 5.16
No smoking status at baseline, n (%)	165 (75.7)	159 (80.3)	168 (80.8)	192 (83.8)
Time since 1st diagnosis of PsA (years)	5.20 ± 7.74	5.93 ± 7.29	5.05 ± 7.47	5.43 ± 7.30
Patients with PsO (BSA ≥ 3%), n (%)	102 (46.8)	94 (47.5)	113 (54.3)	108 (47.2)
Adjusted tender joint total score for PsA (78 joints)	21.4 ± 15.69	22.1 ± 14.89	17.2 ± 11.28	19.3 ± 14.65
Adjusted swollen joint total score for PsA (76 joints)	9.6 ± 7.07	10.4 ± 8.32	9.9 ± 7.55	10.0 ± 7.45
Patient's global assessment (0-100)	65.1 ± 19.85	63.9 ± 20.38	62.8 ± 19.45	60.1 ± 20.95
Physician's global assessment (0-100)	60.7 ± 17.15	62.4 ± 15.42	59.4 ± 17.12	60.5 ± 16.32
PsA Pain (0-100)	60.3 ± 23.30	60.0 ± 22.63	56.7 ± 23.61	56.2 ± 22.14
HAQ-DI	1.44 ± 0.60	1.41 ± 0.60	1.09 ± 0.62	1.08 ± 0.64
CRP ≥ 10 mg/L, n (%)	70 (32.1)	52 (26.3)	61 (29.3)	76 (33.2)
Presence of enthesitis, n (%)	139 (63.8)	133 (67.2)	95 (45.7)	131 (57.2)

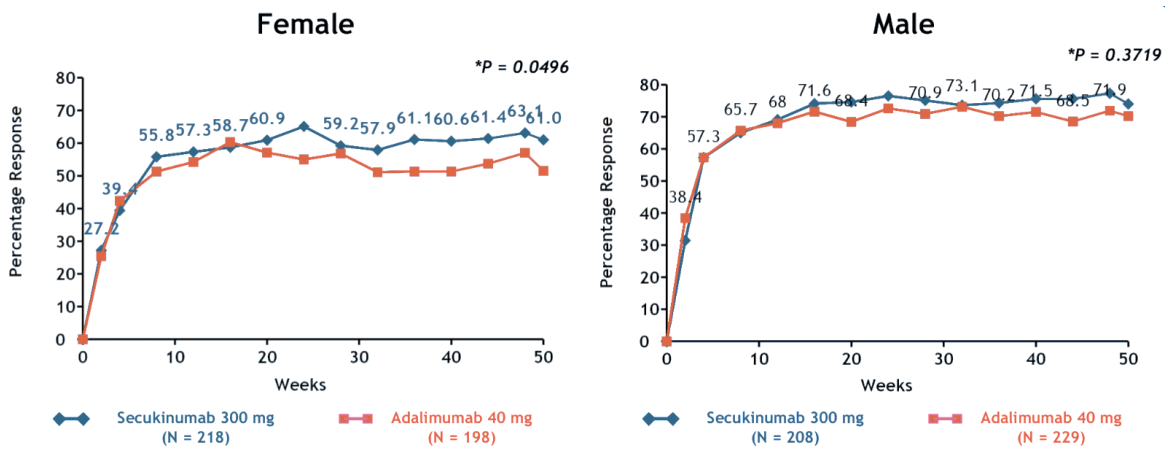
ADA = adalimumab; BSA = body surface area; HAQ-DI = Health Assessment Questionnaire Disability Index; CRP = C-reactive protein; SEC = secukinumab.

Wright GC, et al. Oral Presentation #0507. Presented at ACR Convergence 2020. November 5-9, 2020. All Virtual.

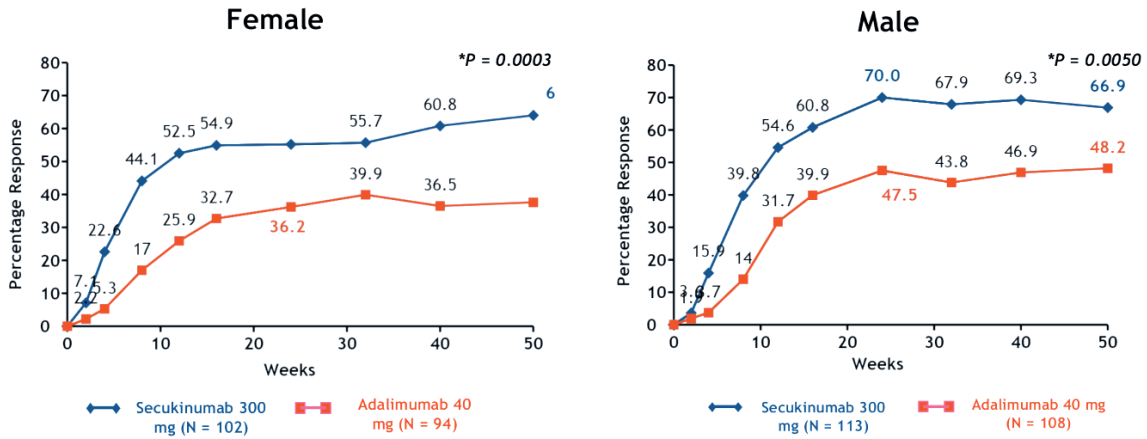
Comparison of Secukinumab vs Adalimumab Efficacy by Sex in PsA

Post-hoc analysis of EXCEED phase 3 trial that evaluated efficacy and safety of secukinumab versus adalimumab as first-line monotherapy in biologic-naïve patients with PsA

ACR 20 Responses



PASI 90 Responses



Similar patterns (women achieving lower/worse outcomes vs men) were observed across other measures, including: changes in baseline for ACR components, HAQ-DI response rates, resolution of enthesitis, DAPSA, PASDAS, LDA, and remission

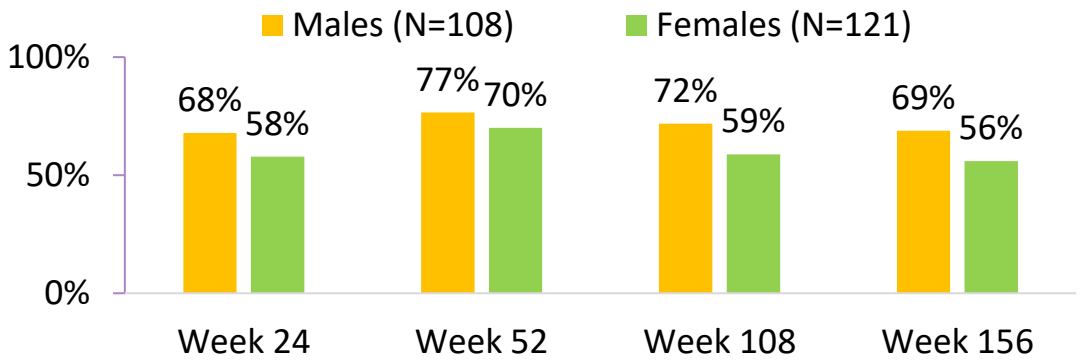
DAPSA = Disease Activity in Psoriatic Arthritis; HAQ-DI = Health Assessment Questionnaire Disability Index; LDA = Low Disease Activity; PASDAS = psoriatic arthritis disease activity score.

Wright GC, et al. Oral Presentation #0507. Presented at ACR Convergence 2020. November 5-9, 2020. All Virtual.

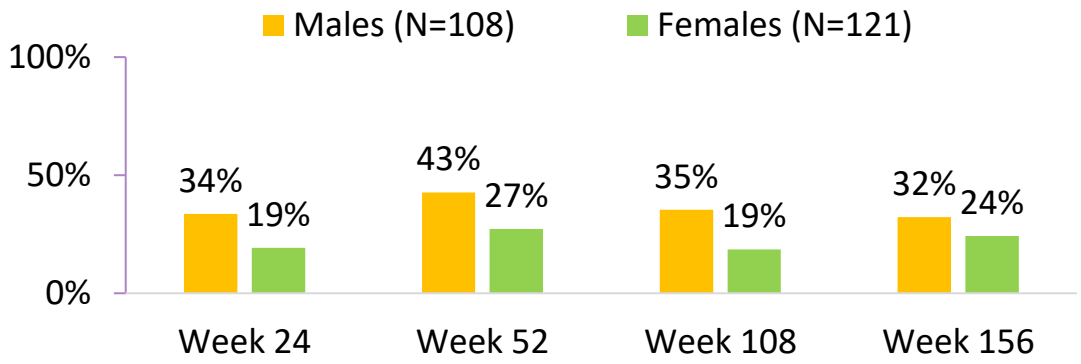
Variable Response to Ixekizumab Between Men & Women PsA Patients

Post-Hoc Analysis of SPIRIT-1 and SPIRIT-2 Phase 3 Trials of Ixekizumab (80mg Q2W and Q4W) in Patients with Active PsA after 3-Years of Treatment

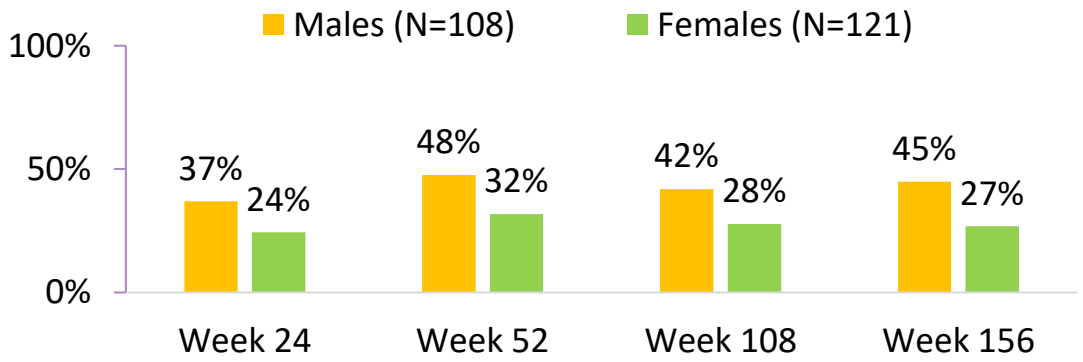
ACR 20 Responses to IXE Q4W



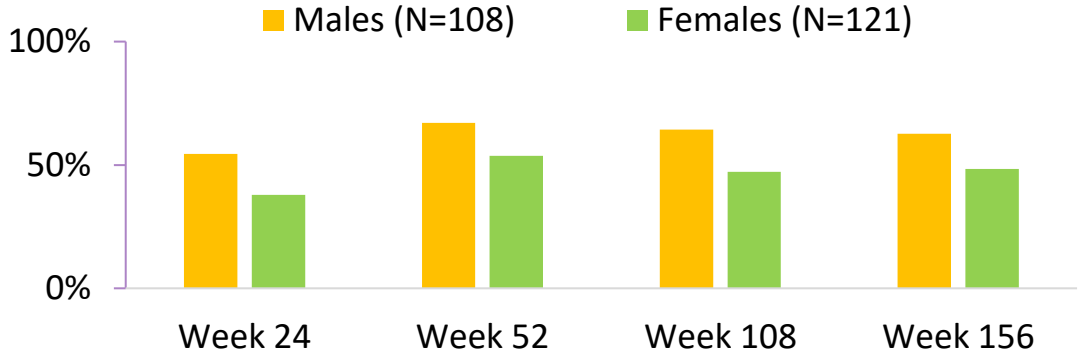
ACR 70 Responses to IXE Q4W



MDA with IXE Q4W



DAPSA LDA with IXE Q4W

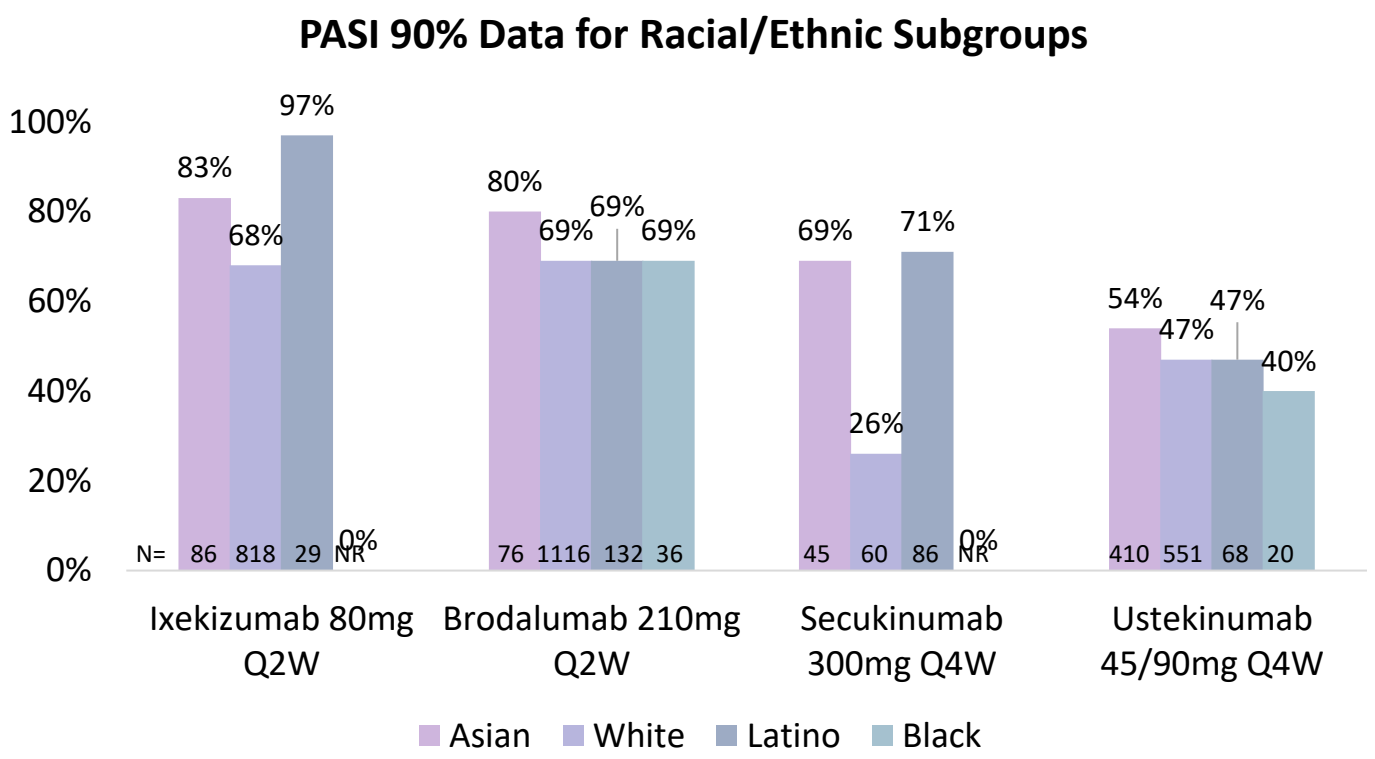


DAPSA LDA = Disease Activity Index for Psoriatic Arthritis, low disease activity; MDA = minimal disease activity.

Eder L, et al. Rheumatol Ther. 2022 Jun;9(3):919-933.

Systematic Review of Racial/Ethnic Differences in Efficacy and Safety of Targeted Therapies for Moderate to Severe PsO

Race/Ethnicity	White	Asian	Latino	Black	Other
Total	9,745	2,740	728	138	140
Age (mean)	45	44	45	45	44
Male	68%	77%	46%	64%	70%
BMI (mean)	30	27	30	31	29
Medication					
Ixekizumab	23%	4%	10%	0%	0%
Secukinumab	2%	3%	26%	0%	0%
Brodalumab	11%	7%	18%	26%	0%
Ustekinumab	6%	30%	9%	15%	0%
Guselkumab	7%	5%	0%	9%	14%
Tildrakizumab	0	4%	0%	0%	0%
BSA %	27	37	33	29	27
PASI (mean)	20	25	23	22	21
DLQI (mean)	13	12	15	17	NR



"The differences in skin clearance **efficacy may be due to differences in weights, genetics, and clinical trial participation** between each race or ethnicity. Regardless… **patients of color are less likely to receive biologics compared to White patients** due to differences in healthcare barriers, perceptions of psoriasis, and differences in treatment identification"

BSA = body surface area; DLQI = Dermatology Life Quality Index; PASI = Psoriasis Area Severity Index.

Ferguson JE, et al. Arch Dermatol Res. 2022 Jan 20.

Wrap Up

Summary

- Reviewed the mechanism of action of IL-17/IL-23 signaling across rheumatic diseases
- Reviewed clinical data of new and emerging therapies targeting the IL-12 and IL-23 pathway
- Reviewed differences in treatment responses for patient subgroups, including by sex and race/ethnicity

IL = interleukin.