Piccole molecole nella terapia della psoriasi (apremilast, upadacitinib, deucravacitinib)

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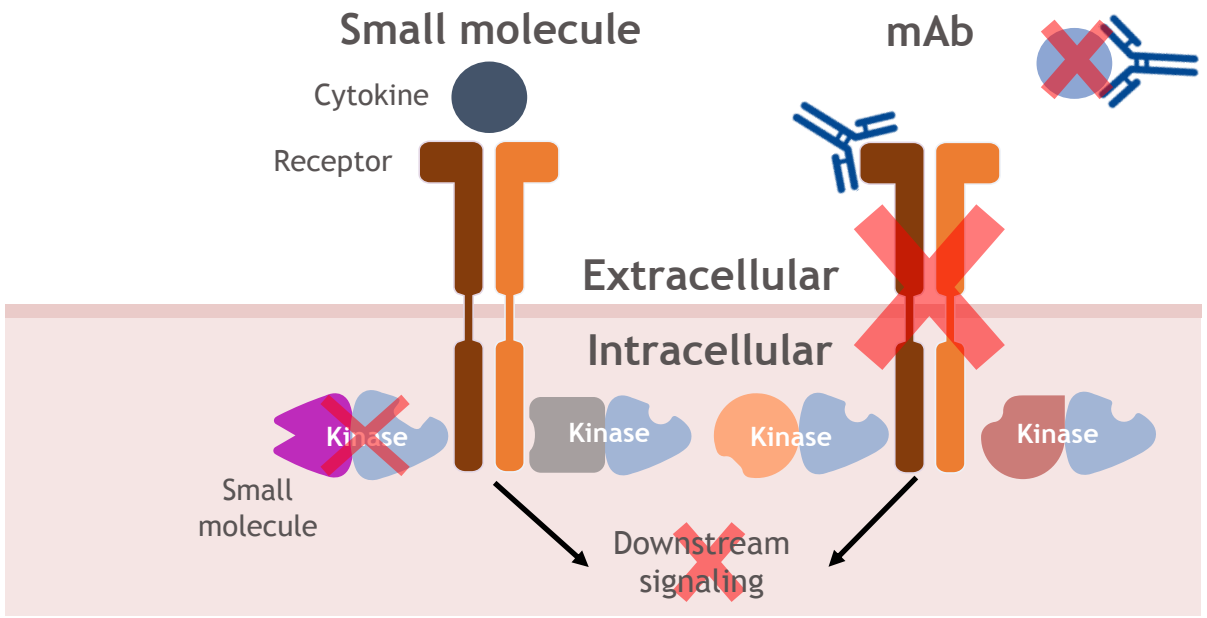
Small-molecule inhibitors vs monoclonal antibodies



Small molecules vs mAbs (biologics): considerations		
	Small molecule	**mAb**
Administration[1-3]	Oral	IV/SC
Half-life[2,3]	Short (e.g. dosed daily or multiple times a day)	Long (e.g. dosed biweekly or monthly)
Target[2,3]	Extra/intracellular	Extracellular
Immunogenicity[1,3]	Non-immunogenic	Neutralizing ADA potential
Toxicity[1,3]	Off-target effects of compound and metabolites	Receptor mediated
Drug interaction[3]	Possible	Rare
Production[1,3]	Chemical synthesis, easy	Biological production, complex

Adapted with permission from *Nat Rev Cancer*,[1] *Mol Cancer*,[2] and *Clin Transl Sci*[3]
ADA, antidrug antibody; IV, intravenous; mAb, monoclonal antibody; SC, subcutaneous.
1. Imai K, Takaoka A. *Nat Rev Cancer*. 2006;6:714-727. 2. Sierra JR et al. *Mol Cancer*. 2010;9:75-88. 3. Ovacik M. *Clin Transl Sci*. 2018;11:540-552.

AGENZIA ITALIANA DEL FARMACO

DETERMINA 14 marzo 2018

Regime di rimborsabilita' e prezzo, a seguito di nuove indicazioni terapeutiche, del medicinale per uso umano [redacted] (Determina n. 416/2018). (18A02291) (GU Serie Generale n.80 del 06-04-2018)

Classificazione ai fini della rimborsabilita'

La nuova indicazione terapeutica del medicinale [redacted]:

Psoriasi

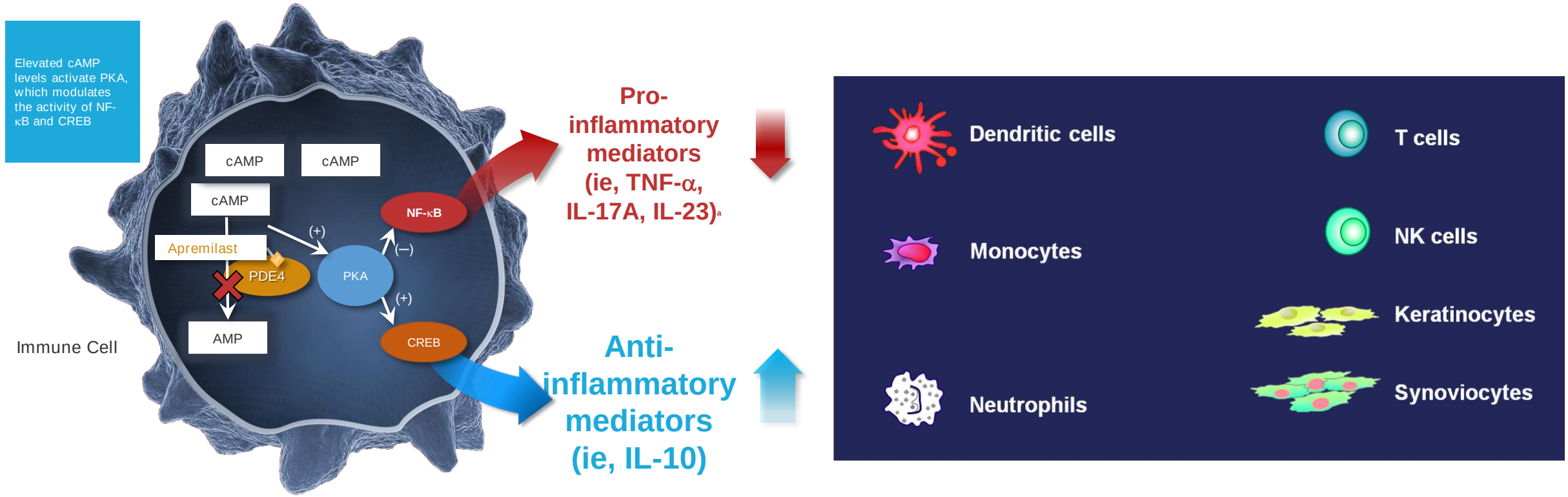
[redacted] e' indicato per il trattamento della psoriasi cronica a placche da moderata a severa in pazienti adulti che non hanno risposto, che hanno una controindicazione o che sono intolleranti ad altra terapia sistemica comprendente ciclosporina, metotrexato o psoralene e raggi ultravioletti di tipo A (PUVA).

e l'indicazione terapeutica:

Artrite psoriasica

[redacted], da solo o in associazione a farmaci antireumatici modificanti la malattia (Disease Modifying Antirheumatic Drugs, DMARD), e' indicato per il trattamento dell'artrite psoriasica (PsA) attiva in pazienti adulti che hanno avuto una risposta inadeguata o sono risultati intolleranti a una precedente terapia con DMARD.

Apremilast MoA: cell-specific PDE4 inhibition



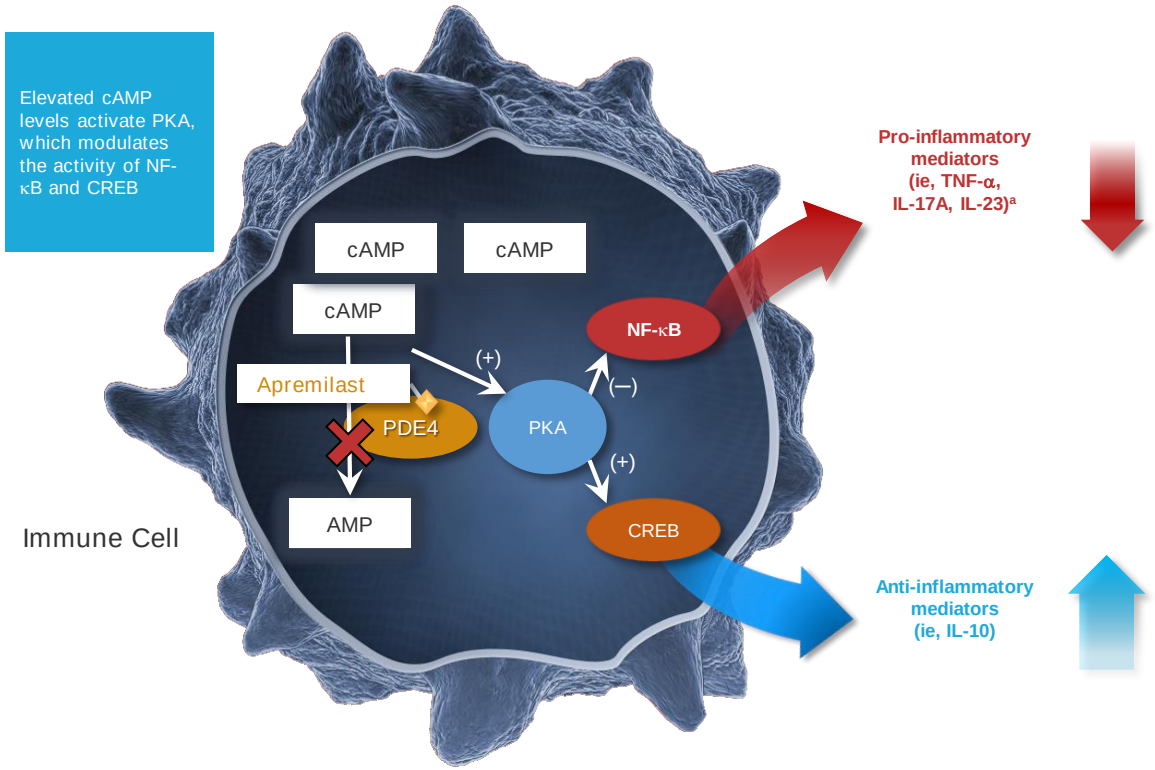
AMP, adenosine monophosphate; cAMP, cyclic adenosine monophosphate; CREB, cAMP response element binding; IL, interleukin; NF-κB, nuclear factor kappa-light-chain-enhancer of activated B cells; PDE4, phosphodiesterase 4; PKA, protein kinase; TNF-α, tumor necrosis factor–alpha.

[a]Based on an exploratory PALACE 1 biomarker substudy of patients with active psoriatic arthritis (n = 150 peripheral blood plasma samples at baseline, weeks 4, 16, 24, and 40) for a total of 47 biomarkers using a validated, multiplexed immunoassay.

1. Schafer PH, et al. J Immunol Res. 2015;2015:906349. 2. van Kuijk AW, et al. Ann Rheum Dis. 2006;65:1551-1557. 3. Ritchlin C, et al. J Rheumatol. 1998;25:1544-1552. 4. Barnas JL, et al. Rheum Dis Clin North Am. 2015;41:643-663. 5. Schafer P. et al. Biochem Pharmacol. 2012;83(12):1583-1590

Wu C, et al. Obes Rev 2016;17:429–41.

Apremilast MoA: cell-specific PDE4 inhibition



PSO & PSA

Ma anche ...

Otezla è indicato per il trattamento di pazienti adulti con ulcere orali associate alla malattia di **Behçet (BD)** che sono candidati alla terapia sistemica.

AMP, adenosine monophosphate; cAMP, cyclic adenosine monophosphate; CREB, cAMP response element binding; IL, interleukin; NF-κB, nuclear factor kappa-light-chain-enhancer of activated B cells; PDE4, phosphodiesterase 4; PKA, protein kinase; TNF-α, tumor necrosis factor–alpha.

[a]Based on an exploratory PALACE 1 biomarker substudy of patients with active psoriatic arthritis (n = 150 peripheral blood plasma samples at baseline, weeks 4, 16, 24, and 40) for a total of 47 biomarkers using a validated, multiplexed immunoassay.

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Wu C, et al. Obes Rev 2016;17:429–41.

APREMILAST È INDICATO PER IL TRATTAMENTO DELLA PSORIASI ED ARTRITE PSORIASICA DA MODERATA A GRAVE

DOSE DI MANTENIMENTO

<u>30 mg per via orale, 2 volte al giorno a distanza di circa 12 ore senza limitazioni per quanto riguarda l'assunzione di cibo [1]</u>

Nei pazienti con grave **compromissione renale***:

- La dose di Apremilast deve essere ridotta a 30 mg 1 volta al giorno [1]
- Si raccomanda di titolare Apremilast utilizzando solo lo schema previsto per la mattina riportato nella tabella qui sopra e di saltare le dosi del pomeriggio.

* Clearance della creatinine inferior a 30 ml al minute, stimata secondo l'equazione di Cockroft-Gault.

OTEZLA® Riassunto delle caratteristiche del prodotto.

PRINCIPALI RISULTATI DI EFFICACIA DI APREMILAST

Una percentuale significativamente maggiore di pazienti ha raggiunto una risposta PASI-75 rispetto al placebo alla settimana 16. La risposta PASI è stata mantenuta a 52 settimane [1]

Apremilast ha apportato un importante miglioramento nel NAPSI e nel ScPGA alla settimana 16. Questi miglioramenti sono stati generalmente manutenuti oltre alla settimana 32 [2]

E’ stato osservato un notevole miglioramento della QoL accompagnato a un rapido e significativo miglioramento del prurito e del dolore [4]

Il 48% dei pazienti con psoriasi palmoplantare da moderata a grave che hanno assunto apremilast (vs 27% con placebo) (punteggio PPPGA basale 3) ha ottenuto il punteggio PPPGA 0 (clear) o 1 (almost clear) alla settimana 16 [3]

Apremilast ha dimostrato efficacia nei segni e sintomi di PsA così come un miglioramento nelle funzioni fisiche e nel HRQOL. I risultati sono sono stati generalmente mantenuti oltre le 52 settimane di trattamento

Sono stati ottenutti maggiori tassi di risposta alla settimana 32 nel punteggio VAS del prurito in pazienti sottoposti a switch da placebo alla settimana 16 [1]

1. Papp K. et al. J Am Acad Dermatol. 2015;73:37-49; 2. Rich P. et al. J Am Acad Dermatol. 2015;74:134 -42; 3. Bissonnette R. et al. J Am Acad Dermatol. 2016;75(1):99-105; 4. Papadavid E. et al. J Eur Acad Dermatol Venereol. 2018;32(7):1173-1179;
5. Mease P. Rheumatol Ther. 2014;1:1-20.

Efficacy of Apremilast in Patients With Moderate to Severe Genital Psoriasis: Body Surface Area Subgroup Results From the Phase 3 DISCREET Trial

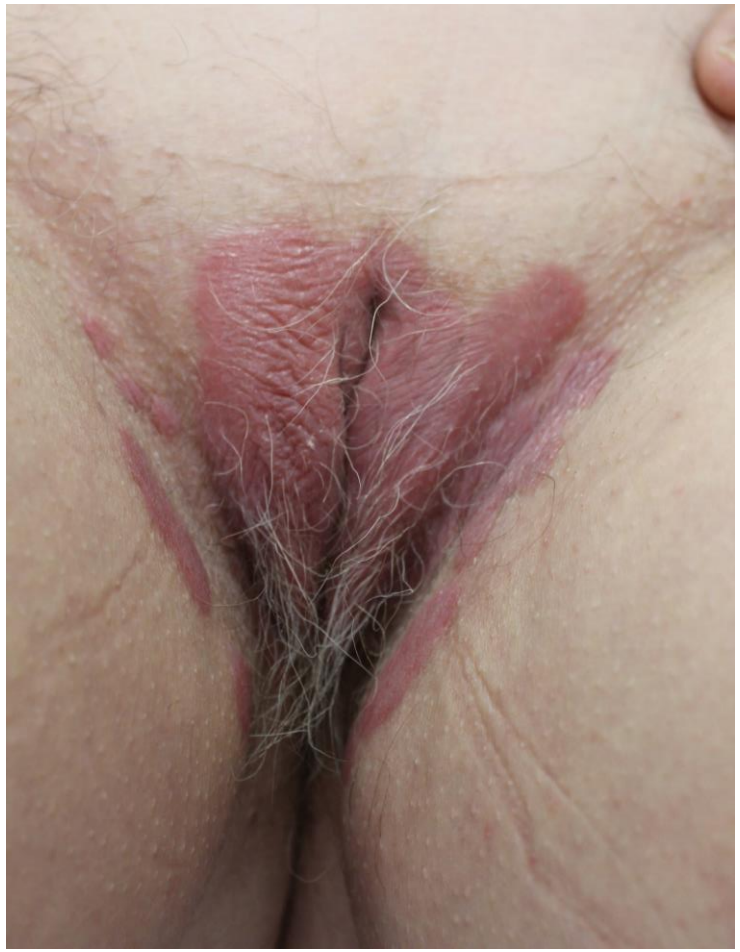
Joseph F. Merola, MD, MMSc[1]; Lawrence Charles Parish, MD, MD (Hon)[2]; Lyn Guenther, MD[3]; Charles Lynde, MD[4,5]; Jean-Philippe Lacour, MD[6]; Petra Staubach, MD[7]; Sue Cheng, MD, PhD[8]; Cynthia Deignan, PhD[8]; Mindy Chen, MS[8]; Kim A. Papp, MD, PhD[9,10]

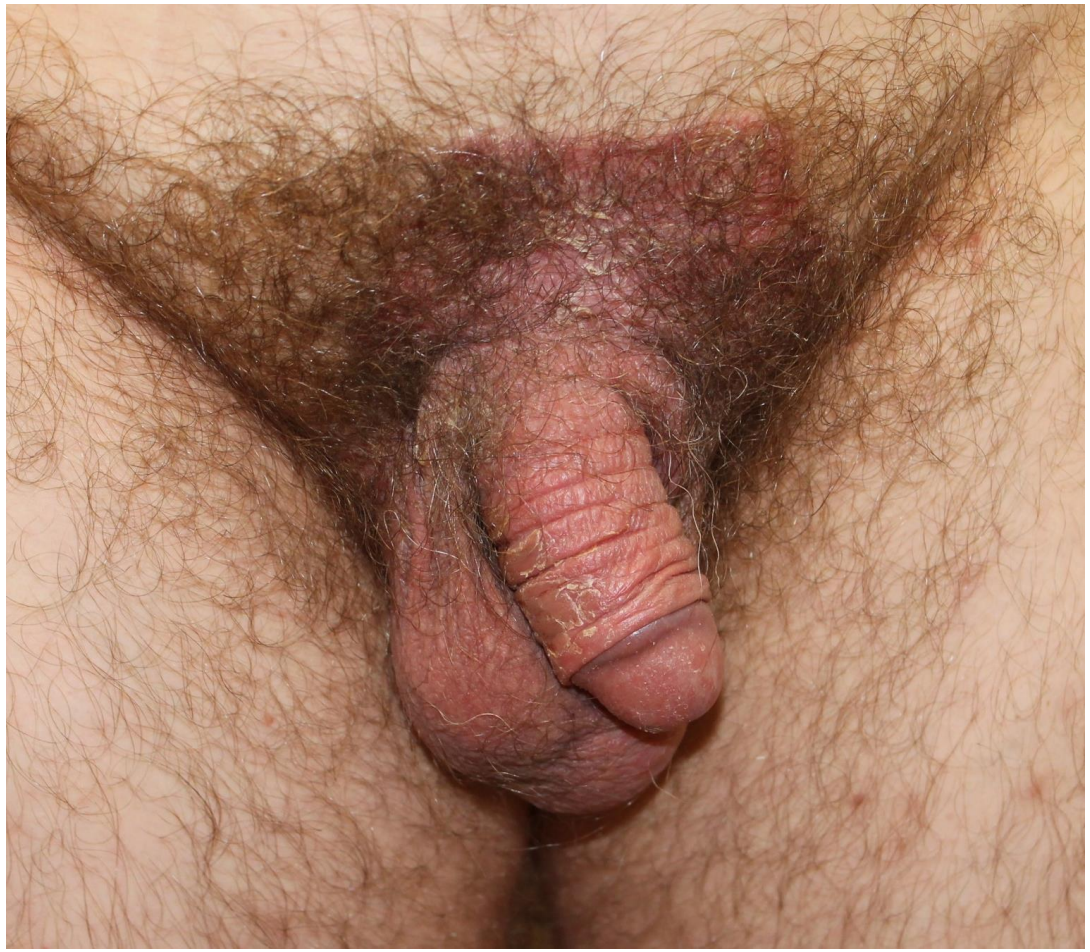
[1]Brigham and Women's Hospital, Harvard Medical School, Boston, MA, USA; [2]Parish Dermatology, Philadelphia, PA, USA; [3]Guenther Research Inc., London, ON, Canada; [4]Lynde Institute for Dermatology, Markham, ON, Canada; [5]Probity Medical Research, Markham, ON, Canada; [6]CHU de Nice - Hôpital l'Archet, Nice, France; [7]Department of Dermatology, University Medical Center, Mainz, Germany; [8]Amgen Inc., Thousand Oaks, CA, USA; [9]Probity Medical Research, Waterloo, ON, Canada; [10]K Papp Clinical Research, Waterloo, ON, Canada

Presented at: the American Academy of Dermatology (AAD) Annual Meeting; March 17–21, 2023; New Orleans, LA.

Background and Objective

- Genital psoriasis, which affects up to 63% of adults with psoriasis, remains highly stigmatized, underdiagnosed, and undertreated[1-3]
- Studies regarding therapies for genital psoriasis are limited, and treatment is challenging[4]





Study Design and Patient Population

- **Design:** Phase 3, multicenter, randomized, double-blind, PBO-controlled, parallel-group study (NCT03777436)
  - Randomization was stratified by baseline BSA < 10% or ≥ 10%
  - A maximum of 60% of patients were to have BSA < 10%
- **Main Inclusion Criteria:** Moderate or severe genital psoriasis (modified static Physician Global Assessment of Genitalia [sPGA-G] score ≥ 3); moderate or severe psoriasis (overall sPGA score ≥ 3); nongenital plaque psoriasis on ≥ 1% of BSA; intolerant to or inadequately controlled by topical therapy for genital psoriasis
- **Primary Endpoint:** Modified sPGA-G response (score of 0 [clear] or 1 [almost clear] with ≥ 2-point reduction from baseline) at Week 16
- **Secondary Endpoints:** sPGA response (score of 0 or 1 with ≥ 2-point reduction from baseline), Genital Psoriasis Itch Numeric Rating Scale (GPI-NRS) response (≥ 4-point improvement), change from baseline in BSA, change from baseline in Dermatology Life Quality Index (DLQI) score, and change from baseline in Genital Psoriasis Symptoms Scale (GPSS) score

Baseline Characteristics

PBO (n=146)		APR (n=143)
46	Mean age, years	44
102 (70)	Male, n (%)	100 (70)
12	Mean duration of genital psoriasis, years	11

Subgroup Analysis

- Efficacy endpoints at Week 16 were analyzed by baseline BSA (< 10% and ≥ 10%)

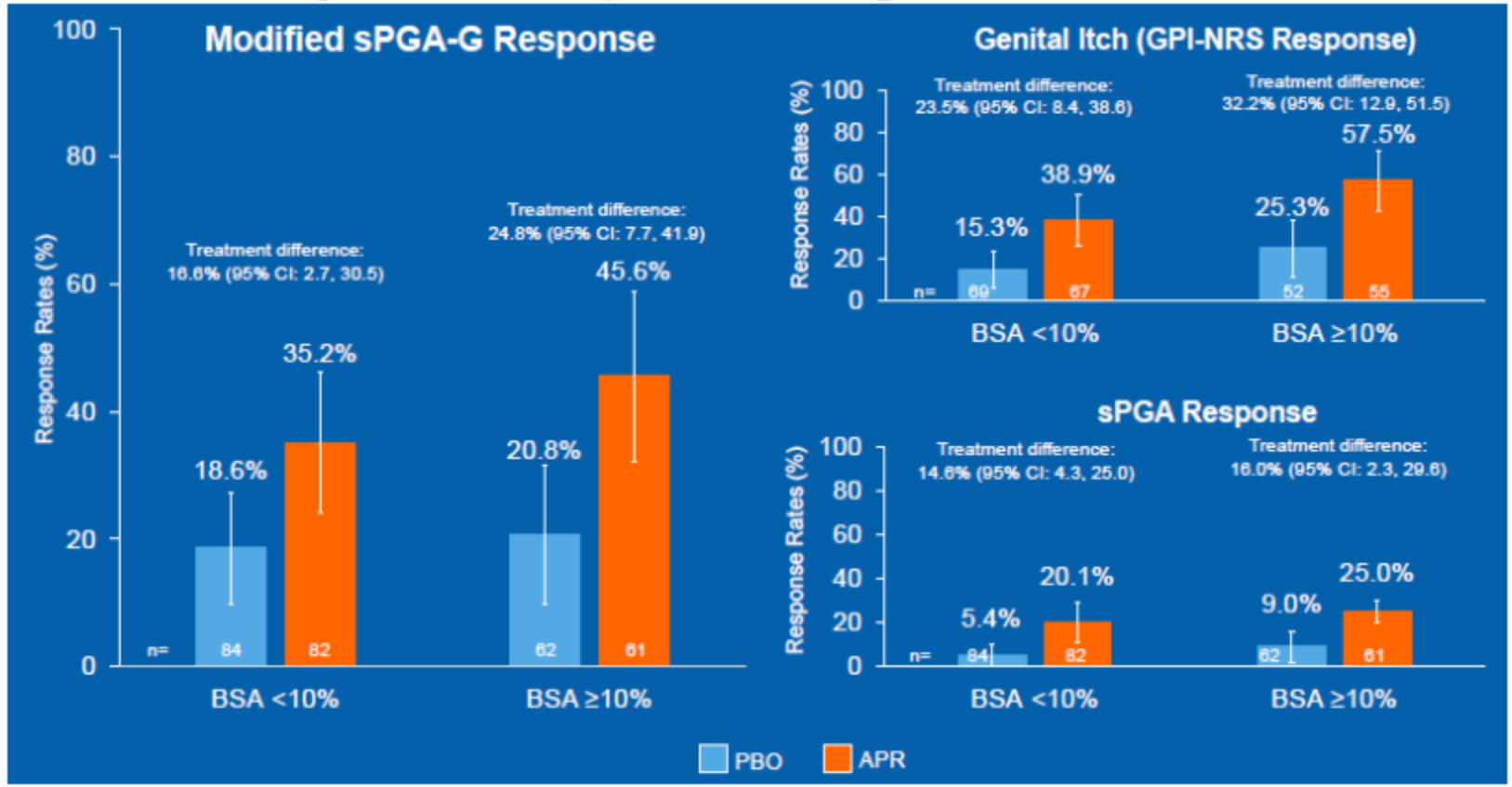
Baseline Disease Characteristics

	BSA <10%		BSA ≥10%	
Score at baseline	PBO n=84	APR n=82	PBO n=62	APR n=61
sPGA-G	3.11	3.12	3.15	3.16
sPGA	3.08	3.06	3.11	3.20
GPI-NRS	6.39	6.42	6.18	7.05
BSA %, mean	5.04	4.57	13.19	19.02
DLQI, mean	11.6	12.0	14.3	14.9
GPSS, mean	41.8	44.7	43.8	49.7

APR = apremilast; BSA = body surface area; DLQI = Dermatology Life Quality Index; GPI-NRS = Genital Psoriasis Itch Numeric Rating Scale; GPSS = Genital Psoriasis Symptoms Scale; PBO = placebo; sPGA = static Physician Global Assessment; sPGA-G = static Physician Global Assessment of Genitalia.

Results

APR patients experienced greater improvements in genital psoriasis symptoms and severity than PBO patients, regardless of baseline BSA



ITT population. Error bars represent 95% CI. Multiple imputation used for missing data. Two-sided *P* values are based on the Cochran-Mantel-Haenszel test. Modified sPGA-G response is defined as a score of 0 (clear) or 1 (almost clear) with ≥ 2-point reduction from baseline. GPI-NRS scores range from 0 (no) to 10 (worst imaginable). sPGA response is defined as a score of 0 (clear) or 1 (almost clear) with ≥ 2-point reduction from baseline.

APR = apremilast; BSA = body surface area; CI = confidence interval; GPI-NRS = Genital Psoriasis Itch Numeric Rating Scale; ITT = intent-to-treat; PBO = placebo; sPGA = static Physician Global Assessment; sPGA-G = static Physician Global Assessment of Genitalia.

American Journal of Clinical Dermatology
https://doi.org/10.1007/s40257-023-00783-7

ORIGINAL RESEARCH ARTICLE

Apremilast Long-Term Safety Up to 5 Years from 15 Pooled Randomized, Placebo-Controlled Studies of Psoriasis, Psoriatic Arthritis, and Behçet's Syndrome

Philip J. Mease[1] · Gülen Hatemi[2] · Maria Paris[3] · Sue Cheng[3] · Peter Maes[3] · Wendy Zhang[3] · Rebecca Shi[3] · Andrea Flower[3] · Hernan Picard[3] · Linda Stein Gold[4]

Accepted: 4 April 2023

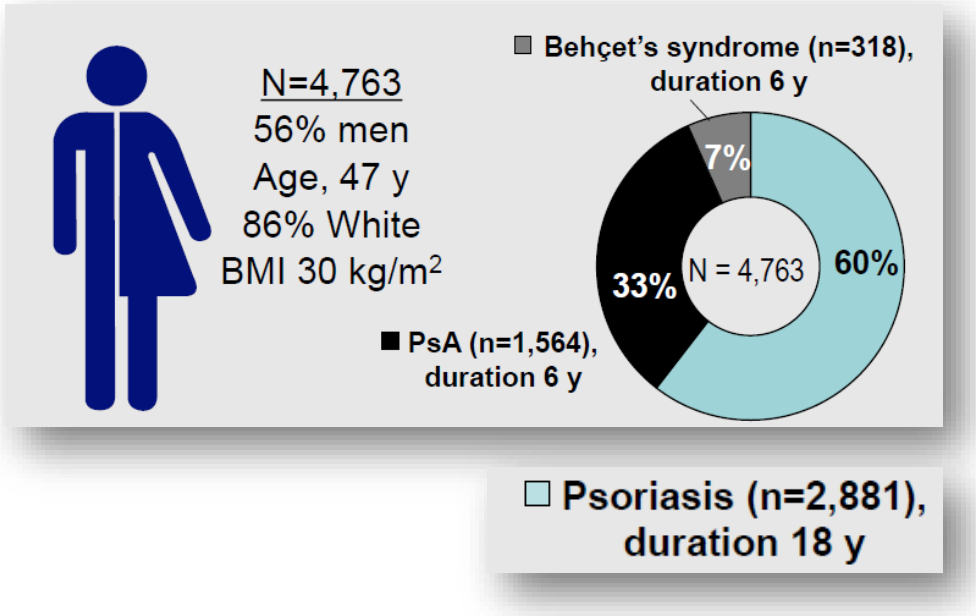
Background and rationale

- Apremilast is an oral phosphodiesterase 4 inhibitor that, as of March 20, 2022, has been used by **706,585 patients** (557,379 patient-years of exposure) worldwide
- Psoriasis, psoriatic arthritis, and Behçet's syndrome are chronic systemic diseases associated with **comorbidities** and increased risk of cardiovascular and thrombotic events
- It is important to evaluate the **long-term safety** of systemic treatments in patients who are at risk for comorbid conditions.
- This long-term pooled safety analysis assessed adverse events (AEs) of **special interest**, including thrombotic events, malignancies, major adverse cardiac events (MACE), serious infections, and depression

STUDY DESIGN AND PATIENT DEMOGRAPHICS

- **Design:** Data from up to 5 years of exposure to apremilast 30 mg BID (APR) were pooled from **15** randomized, placebo (PBO)-controlled studies across indications and divided into PBO-controlled and all-APR-exposure groups
  - **Psoriasis** (8 studies)
  - **PsA** (5 studies)
  - **Behçet's** syndrome (2 studies)
- **Patients:** Adults who met respective study eligibility criteria and received ≥ 1 dose of PBO or APR (PBO-controlled group) or ≥ 1 dose of APR (all-APR-exposure group) were assessed for safety

- During the PBO-controlled periods, **2,676** patients were randomized to APR and **2,087** were randomized to PBO
- Of the 4,763 patients included in the analysis, **4,183** patients were exposed to APR (6,788 patient-years [PY])



Results

Table 3 Overview of safety and commonly reported TEAEs

	Placebo-controlled period				All apremilast exposure	
	Placebo [$n = 2084$] 622.2 patient-years		Apremilast 30 mg bid [$n = 2673$] 848.8 patient-years		Apremilast 30 mg bid [$n = 4183$] 6788.0 patient-years	
	n (%)	EAIR/100 patient-years	n (%)	EAIR/100 patient-years	n (%)	EAIR/100 patient-years
Any TEAE	1113 (53.4)	279.1	1780 (66.6)	433.5	3265 (78.1)	179.5
Common TEAEs (≥5% of patients)						
Diarrhea	123 (5.9)	20.6	481 (18.0)	66.1	759 (18.1)	13.1
Nausea	115 (5.5)	19.1	432 (16.2)	58.5	665 (15.9)	11.3
Headache	121 (5.8)	20.2	282 (10.5)	36.0	470 (11.2)	7.6
URTI	96 (4.6)	15.8	178 (6.7)	21.7	537 (12.8)	9.0
Nasopharyngitis	93 (4.5)	15.3	153 (5.7)	18.6	491 (11.7)	8.1
Arthralgia	39 (1.9)	6.3	53 (2.0)	6.3	227 (5.4)	3.5
Hypertension	46 (2.2)	7.5	50 (1.9)	6.0	211 (5.0)	3.3

TEAEs in the APR-Exposure Period

- **Most TEAEs were mild or moderate, and rates of TEAEs leading to drug withdrawal were low during the APR-exposure period**
- **Common TEAEs were consistent with those previously reported in the individual clinical trials**

Pooled Population Exposure

- **Overall APR exposure: 6,788.0 PY**
- **Median APR exposure: 51 weeks (range: 0.1–316.1)**

TEAEs in the PBO-Controlled Period

- **Most TEAEs were mild or moderate, and rates of TEAEs leading to drug withdrawal were low during the PBO-controlled period**
- **Gastrointestinal TEAEs were largely mild or moderate, usually began within the first 1 to 2 weeks of APR treatment, and typically resolved within 30 days**

Results

Incidence rates of serious TEAEs and TEAEs of special interest were low and similar between PBO and APR groups in the PBO-controlled period, and remained low throughout the APR-exposure period

MACE (0.3)

Thrombotic events (0.1)*

Malignancies (1.0)†

Serious infections (1.1)

Serious opportunistic infections (0.2)

Depression (1.8)

Values in parentheses represent EAIRs per 100 patient-years for special interest TEAEs through the APR-exposure period

No new safety signals were identified through 5 years

90%

Most TEAEs (>90%) were **mild to moderate** in severity in the PBO-controlled period and throughout all APR exposure

Safety findings were **consistent** across indications and regions

Conclusion

EAIRs for serious events and events of special interest were low in patients treated with APR despite long-term exposure

These results further establish the long-term safety profile of APR across the approved indications of PsO, PsA, or Behçet's syndrome

ORAL PRESENTATION # D1T01.3E

Efficacy and Safety of Apremilast in Pediatric Patients With Moderate to Severe Plaque Psoriasis: 16-Week Results From a Phase 3, Randomized, Double-Blind, Placebo-Controlled Study

Loretta Fiorillo, MD[1]; Emily Becker, MD[2]; Raul de Lucas, MD[3]; Anna Belloni-Fortina, MD[4]; Susana Armesto, MD[5]; Peter Maes, BA[6]; Rajneet K. Oberoi, BPharm, PhD[6]; Maria Paris, MD[6]; Wendy Zhang, MD, MSc[6]; Zuoshun Zhang, PhD[6]; Lisa Arkin, MD[7]

[1]Stollery Children's Hospital University of Alberta, Edmonton, Alberta, Canada; [2]Driscoll Children's Hospital, Corpus Christi, TX, USA; [3]Hospital Universitario La Paz – PPDS, Madrid, Spain; [4]Azienda Ospedale Università Padova, Padova, Italy; [5]Hospital Universitario Marques de Valdecilla, Santander, Spain; [6]Amgen Inc., Thousand Oaks, CA, USA; [7]University of Wisconsin School of Medicine and Public Health, Madison, WI, USA

Presented at: 31st European Academy of Dermatology and Venereology (EADV) Congress; September 7–10, 2022; Milan, Italy and Virtual Meeting.

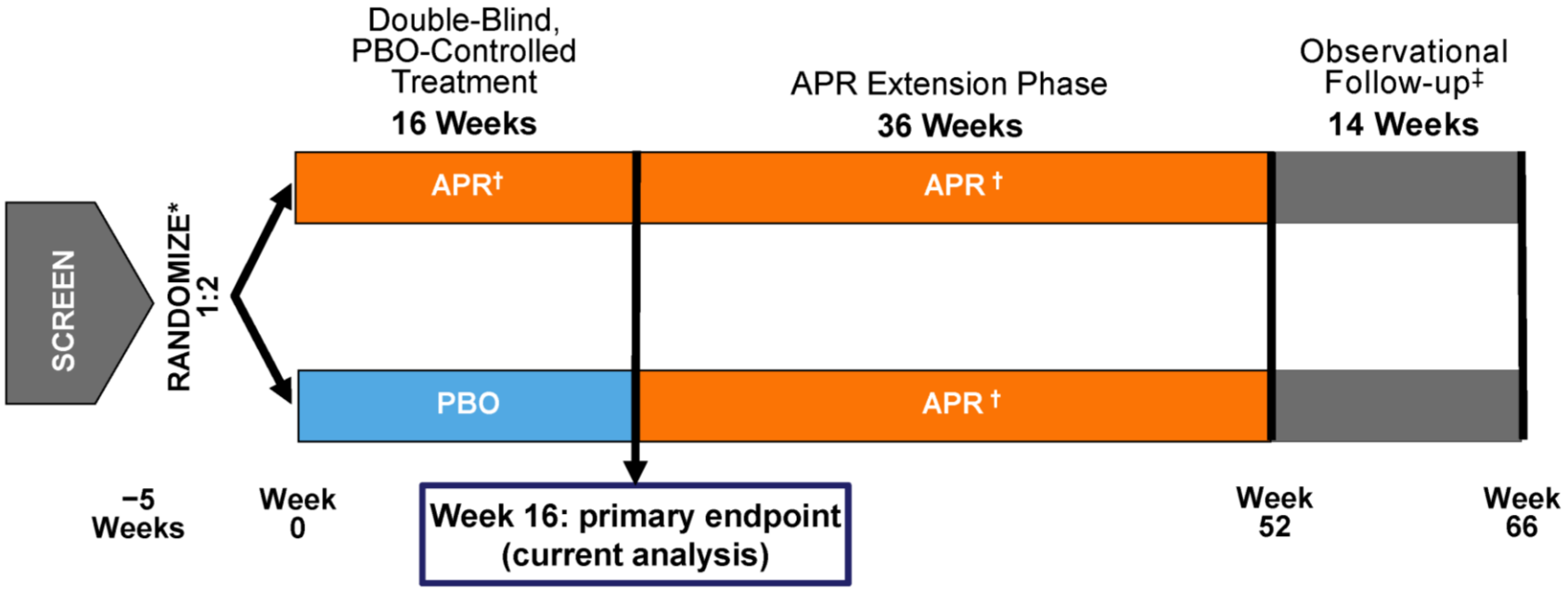
METHODS

- **Main inclusion criteria:**
  - Aged 6 to 17 years
  - Moderate to severe plaque psoriasis (PASI ≥12, BSA ≥10%, and sPGA ≥3)
  - Inadequately controlled by or inappropriate for topical therapy
- **Assessments:**
  - The primary endpoint was sPGA response (score of 0 [clear] or 1 [almost clear] with a ≥2-point reduction from baseline) at Week 16
  - The major secondary endpoint was the proportions of patients achieving PASI-75 at Week 16
  - Endpoints were assessed both in the ITT population and by baseline age and weight subgroups

BSA = body surface area; ITT = intent-to-treat; PASI = Psoriasis Area and Severity Index; PASI-75 = a ≥75% reduction in PASI score; sPGA = static Physician Global Assessment.

SPROUT STUDY DESIGN

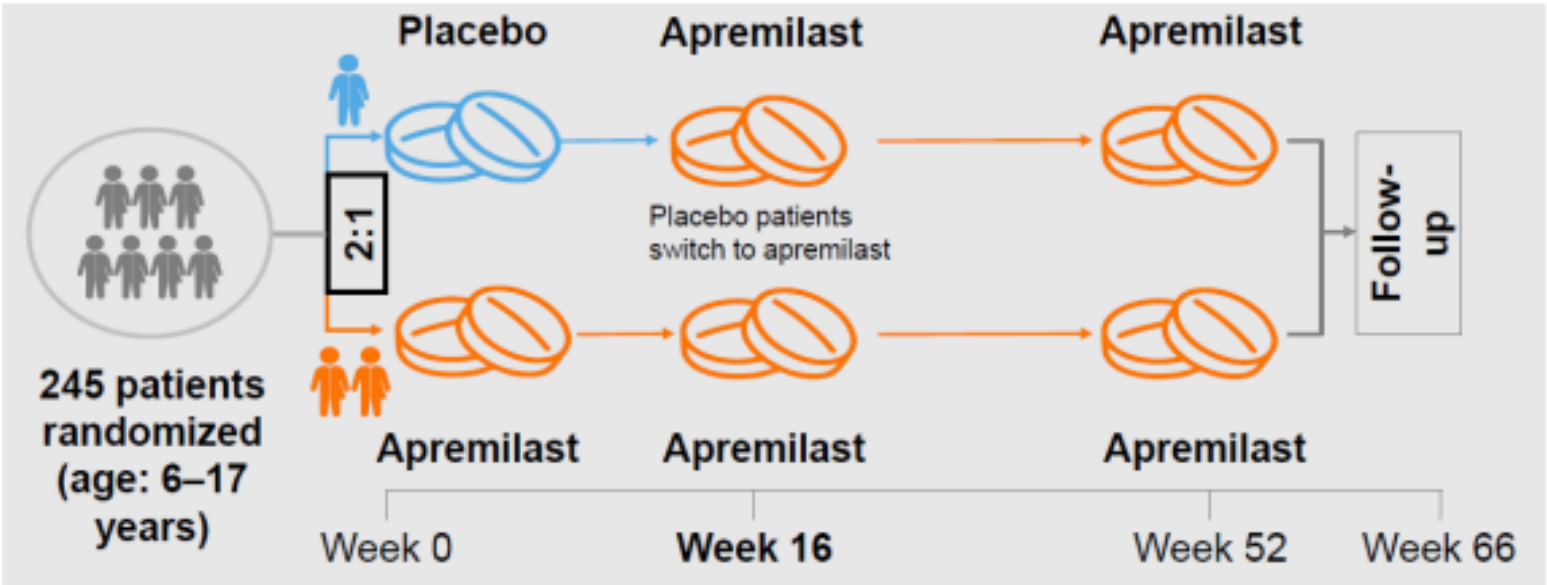
- Phase 3, multicenter, randomized, double-blind, PBO-controlled, parallel study (NCT03701763)



*Randomization was stratified by age group.
†Patients weighing ≥20 to <50 kg received APR 20 mg BID and patients weighing ≥50 kg received APR 30 mg BID.
‡For patients who (1) completed the study and opted not to continue in the long-term study or (2) discontinued the study early.
PBO = placebo.

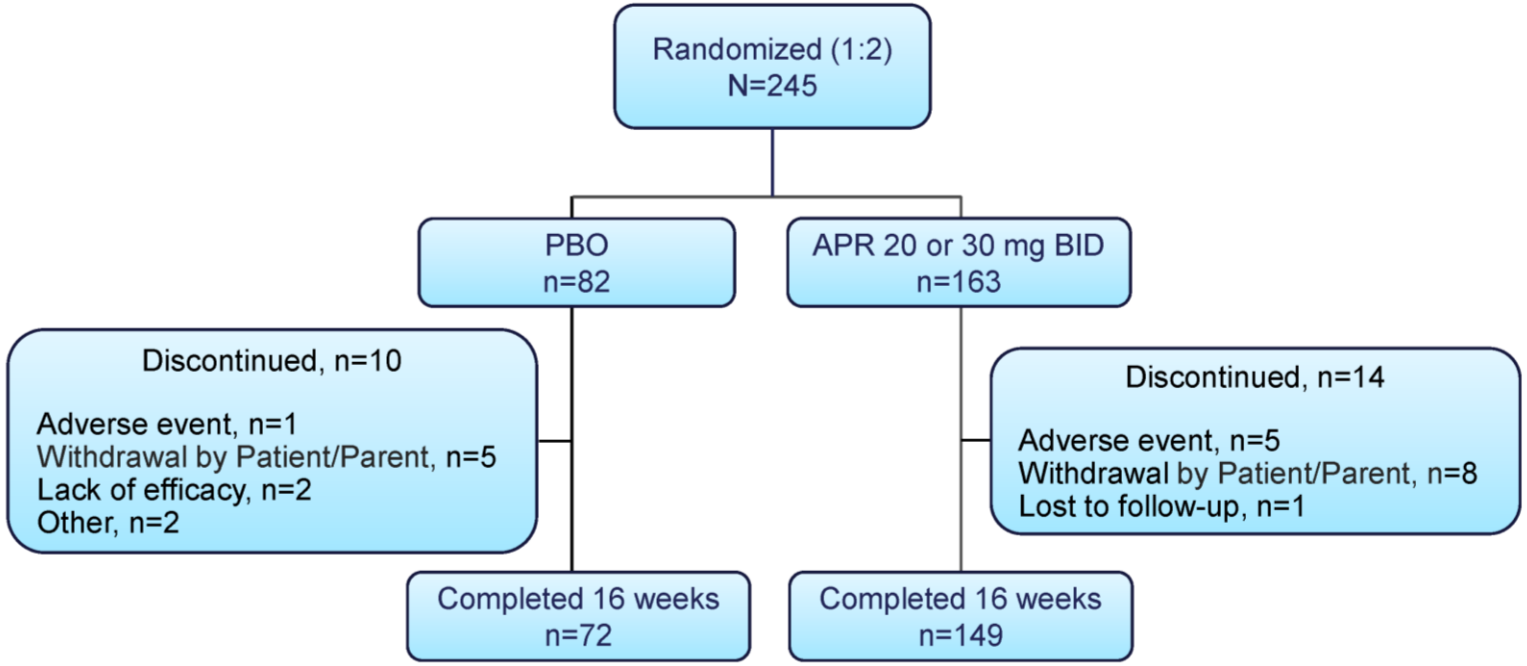
Study Design and Patient Population

- **Design:** Phase 3, multicenter, randomized, double-blind, PBO-controlled, parallel-group study (NCT03701763)
  - Randomization (2:1) was stratified by age group
  - Patients weighing ≥ 20 to < 50 kg received APR 20 mg BID; patients weighing ≥ 50 kg received APR 30 mg BID



PATIENT DISPOSITION

- 245 patients were randomized from December 2018 to December 2021
- Of these, 90% completed the 16-week double-blind period

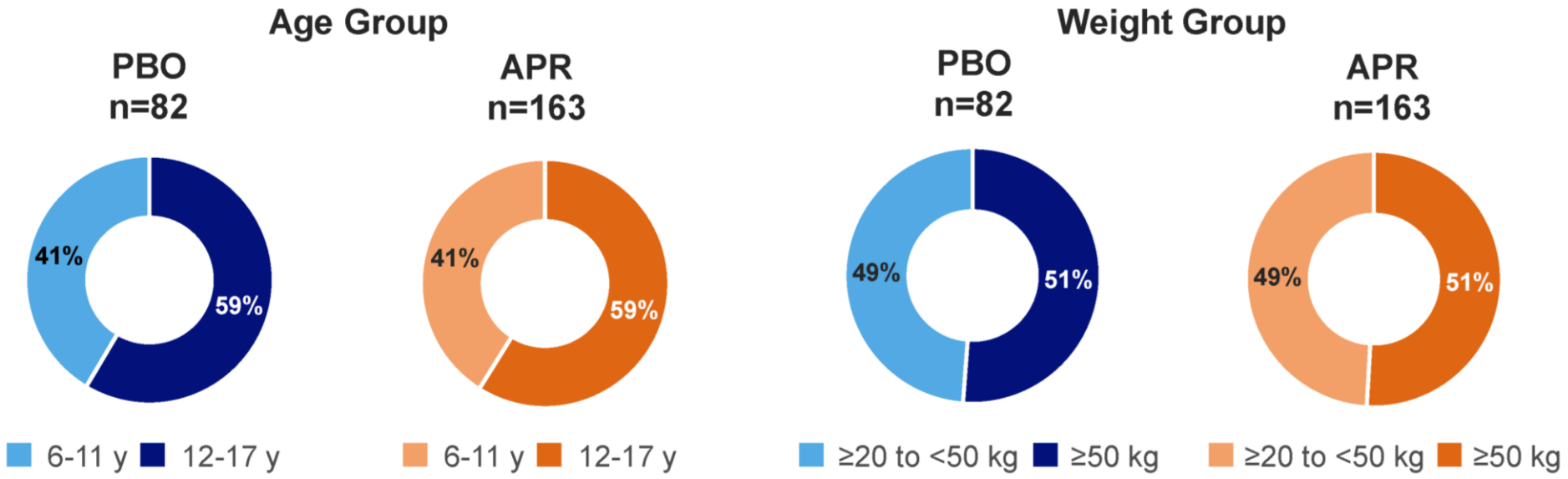


BASELINE DEMOGRAPHICS AND DISEASE CHARACTERISTICS WERE WELL BALANCED

Demographic/characteristic	PBO (n=82)	APR (n=163)	Total (N=245)
Age, mean (SD), y	12.2 (3.3)	12.3 (3.3)	12.2 (3.3)
Female, n (%)	39 (47.6)	89 (54.6)	128 (52.2)
Weight, mean (SD), kg	51.8 (22.2)	52.0 (21.1)	52.0 (21.4)
BMI, mean (SD), kg/m²	21.3 (5.6)	21.3 (5.2)	21.3 (5.3)
Duration of plaque psoriasis, mean (SD), y	4.0 (3.4)	4.3 (3.3)	4.2 (3.4)
sPGA score, n (%)			
3 (Moderate)	63 (76.8)	122 (74.8)	185 (75.5)
4 (Severe)	19 (23.2)	41 (25.2)	60 (24.5)
PASI, mean (SD)	19.5 (8.0)	20.0 (8.2)	19.8 (8.1)
BSA, mean (SD), %	30.8 (19.0)	31.9 (18.5)	31.5 (18.6)

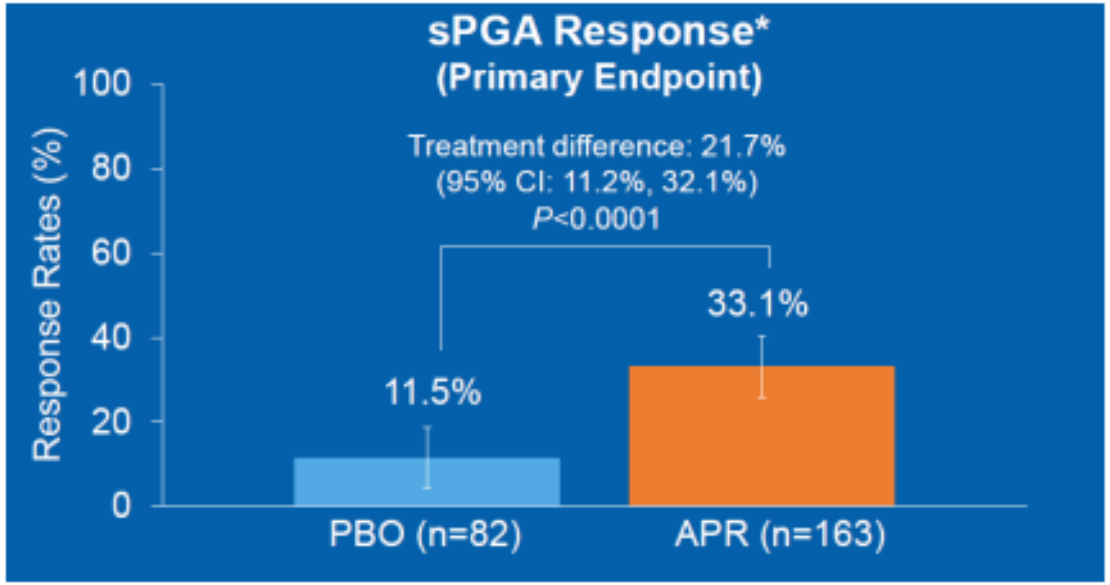
BMI = body mass index.

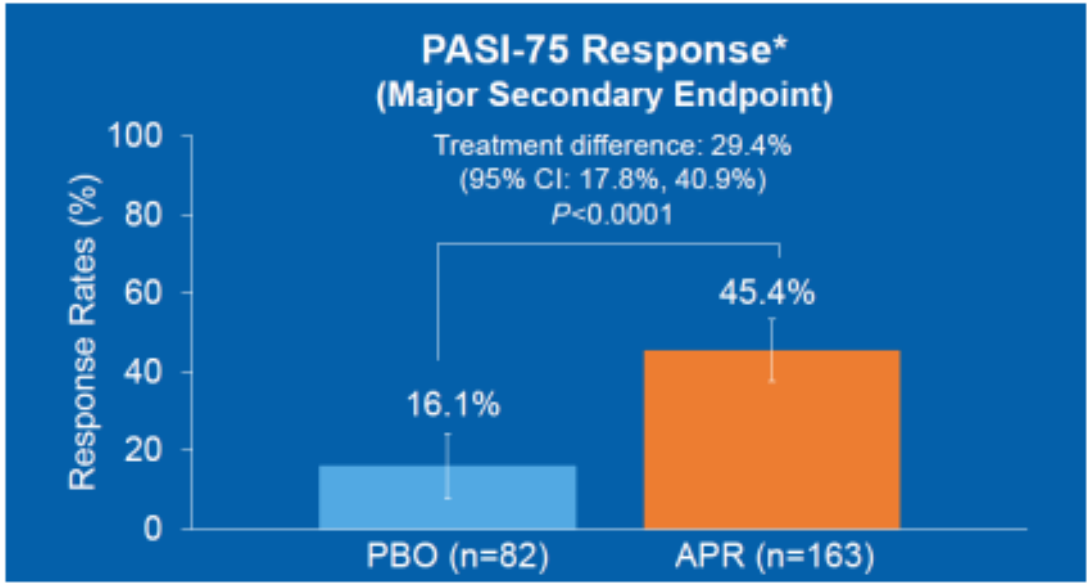
AGE AND WEIGHT SUBGROUPS WERE WELL BALANCED



RESULTS

sPGA and PASI-75 response rates at Week 16 were nearly 3 times greater in patients receiving APR versus PBO



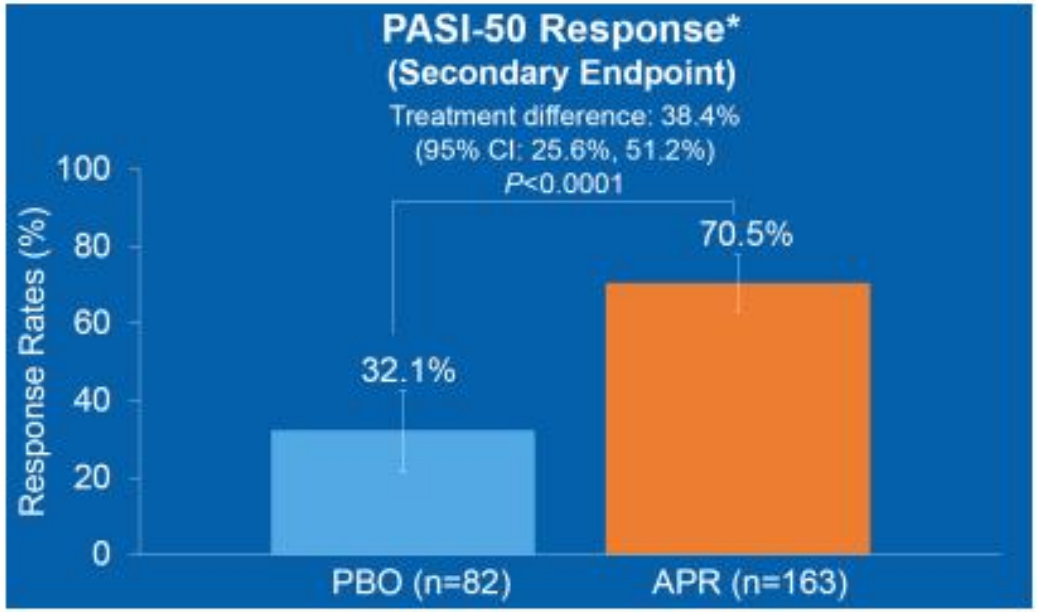


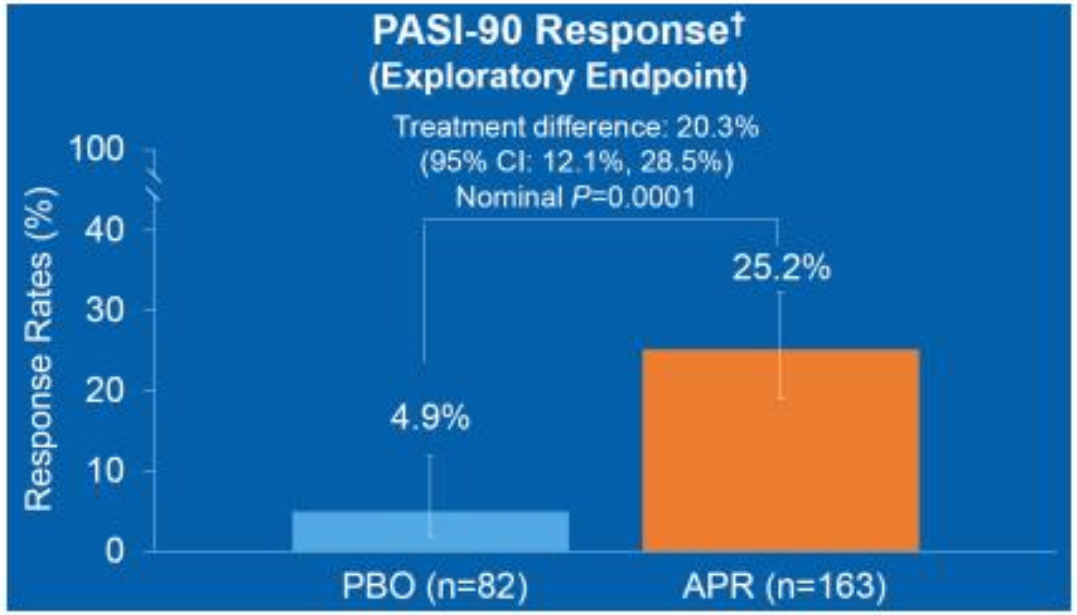
- Results were consistent among subgroups of patients weighing ≥ 20 kg to < 50 kg at baseline (receiving APR 20 mg BID) and patients weighing ≥ 50 kg at baseline (receiving APR 30 mg BID) *(scan QR code)*

Intent-to-treat population. Error bars represent 95% CI. *Missing values imputed using multiple imputation. sPGA response is defined as sPGA score of 0 (clear) or 1 (almost clear) with a ≥ 2-point reduction from baseline. PASI-75 response is defined as ≥ 75% reduction in total PASI score from baseline. Two-sided *P* value is based on the Cochran-Mantel-Haenszel test adjusting for the stratification factors.

RESULTS

Other PASI response rates were significantly greater for APR patients at Week 16

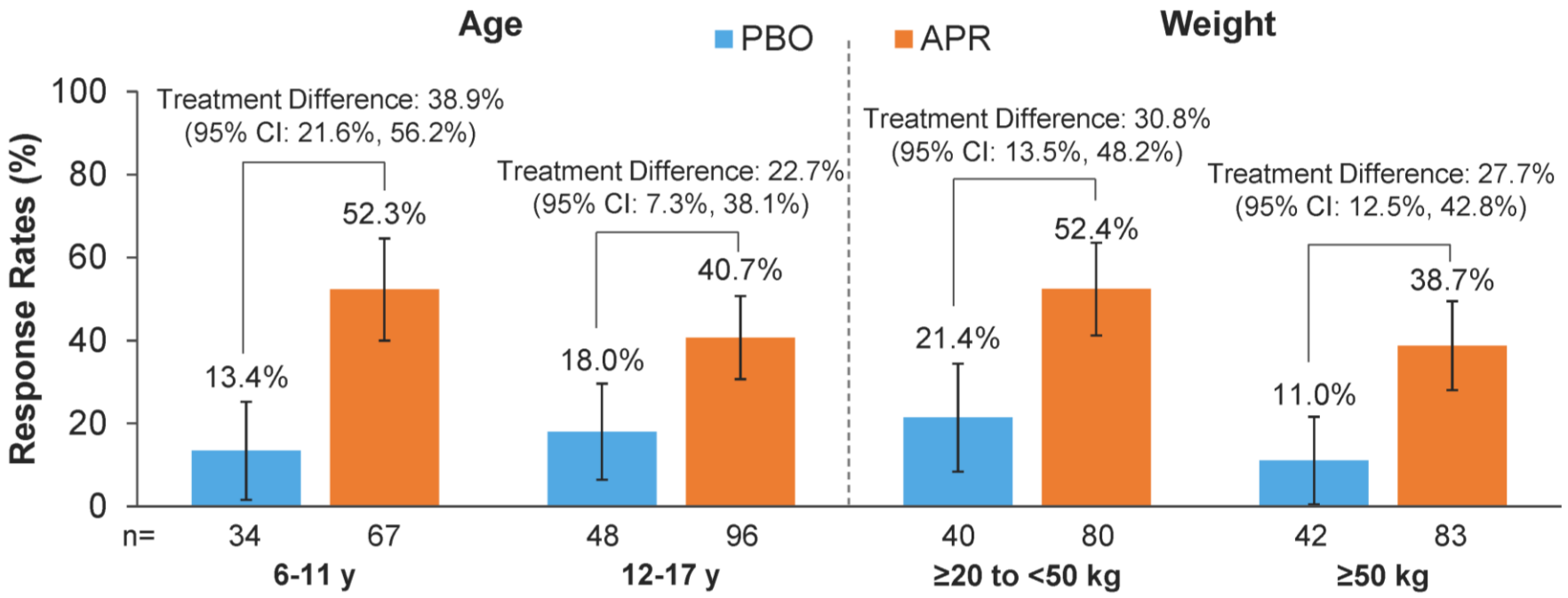




Intent-to-treat population. Error bars represent 95% CI. *Missing values imputed using multiple imputation. †Missing values imputed using last observation carried forward method. PASI-50 response is defined as ≥ 50% reduction in total PASI score from baseline. PASI-90 response is defined as ≥ 90% reduction in total PASI score from baseline. Two-sided *P* value is based on the Cochran-Mantel-Haenszel test adjusting for the stratification factors.

PASI-75 RESPONSE BY AGE AND WEIGHT AT WEEK 16

- Significantly more patients achieved a PASI-75 response with APR vs PBO regardless of age or weight



Intent-to-treat population. Error bars represent 95% CI. Missing values imputed using multiple imputation.

THE OVERALL SAFETY PROFILE WAS CONSISTENT WITH PRIOR STUDIES

Few TEAEs led to withdrawal of the study drug. Reasons included primarily gastrointestinal disorders for APR and suicidal ideation for PBO.

The most common TEAE was diarrhea. 70% of events in the APR group resolved within 3 days during the PBO-controlled period.

Overview of TEAEs and Most Commonly Reported TEAEs (Weeks 0 to 16)		
Patients, n (%)	**PBO (n=80)**	**APR (n=163)**
Any TEAE	33 (41.3)	106 (65.0)
Any drug-related TEAE	12 (15.0)	68 (41.7)
Any severe TEAE	1 (1.3)	2 (1.2)
Any serious TEAE	1 (1.3)	2 (1.2)
TEAE leading to drug withdrawal*	1 (1.3)	5 (3.1)
TEAEs occurring in ≥5% of patients		
Diarrhea†	8 (10.0)	33 (20.2)
Nausea	2 (2.5)	32 (19.6)
Abdominal pain	8 (10.0)	32 (19.6)
Vomiting	2 (2.5)	29 (17.8)
Headache	4 (5.0)	17 (10.4)
Pyrexia	1 (1.3)	11 (6.7)
Nasopharyngitis	3 (3.8)	10 (6.1)
Abdominal pain upper	4 (5.0)	9 (5.5)
COVID-19	5 (6.3)	5 (3.1)

Safety population. *Few TEAEs led to withdrawal of the study drug. Reasons included primarily gastrointestinal disorders for APR and suicidal ideation for PBO. †The most common TEAE was diarrhea. 70% of events in the APR group resolved within 3 days during the PBO-controlled period.

TEAE = treatment-emergent adverse event.

1. Papp K, et al. *J Am Adad Dermatol*. 2015;73:37-49. 2. Paul C, et al. *Br J Dermatol*. 2015;173:1387-1399.

Effects of Apremilast on Changes in Cardiometabolic Parameters by Diabetes and Obesity Status in Patients With Psoriatic Arthritis

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Background and Objective

- Patients with psoriatic arthritis (PsA) have a greater burden of cardiometabolic diseases, including obesity and diabetes, compared with the general population[1,2]
- Phosphodiesterase 4 (PDE4) mediates a broad range of inflammatory and metabolic processes, including glucose metabolism and adipocyte function[3]
- Apremilast (APR) is a unique PDE4 inhibitor approved for the treatment of PsA
  - APR is associated with weight loss and a reduction in glycated hemoglobin (HbA1c)[4–6]
- **Objective:** To evaluate the effects of APR on cardiometabolic parameters over 52 weeks in patients with active PsA from five pooled phase 3 trials

Study Design and Patient Population

- **Design:** Data from five randomized, placebo-controlled, phase 3 studies (PALACE 1–4 and ACTIVE)[7–11] were pooled
- **Patients:** Patients with active PsA who were treated with APR 30 mg BID for 52 weeks
- **Assessments:** Changes from baseline to week 52 in body mass index (BMI), HbA1c, and low- and high-density lipoprotein (LDL, HDL) were assessed and stratified by baseline level of these parameters and week 52 disease activity (Clinical Disease Activity Index for Psoriatic Arthritis [cDAPSA] remission/low disease activity [REM/LDA] vs moderate/high disease activity [ModDA/HDA])
  - Cutoffs for cardiometabolic parameter categories followed standards used by the Cleveland Clinic

Baseline Characteristics

Characteristic	APR (n = 781)
Age*, mean (SD), years	50.1 (11.8)
Female*, n (%)	427 (54.7)
BMI†, mean (SD), kg/m^2	30.3 (6.6)
HbA1c†, mean (SD), %	5.6 (0.6)
LDL†, mean (SD) mg/dL	119.6 (34.5)
HDL†, mean (SD) mg/dL	55.0 (16.5)

*Includes patients who received ≥1 dose of APR. †Includes patients who had both baseline and week 52 values. APR, apremilast; BMI, body mass index; HbA1c, glycated hemoglobin; HDL, high-density lipoprotein; LDL, low-density lipoprotein; SD, standard deviation.

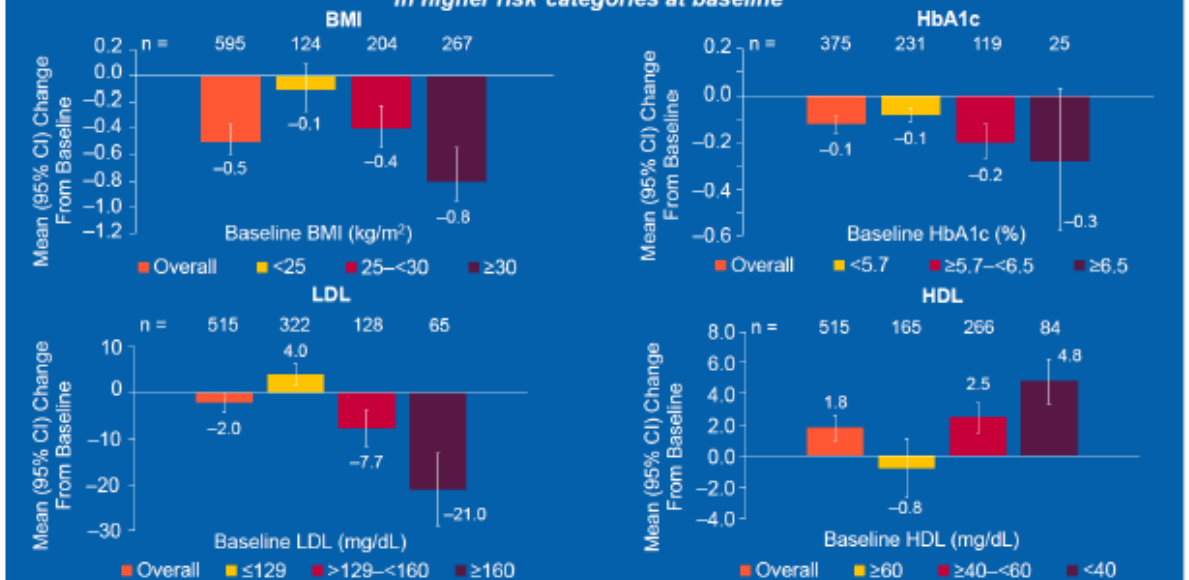
Changes by Week 52 cDAPSA Category

- Greater changes in cardiometabolic parameters were seen in patients with higher baseline BMI, HbA1c, or LDL and lower HDL regardless of whether REM/LDA was achieved at week 52

Key Takeaways

- **APR treatment was associated with improvement in cardiometabolic parameters observed across psoriatic disease activity groups.**
- **The most favorable changes were seen in patients with high LDL, low HDL, obesity, or diabetes at baseline.**
- **These findings suggest that patients with a high burden of comorbid cardiometabolic diseases and active PsA treatment may gain benefit beyond joint disease with APR. However, these findings require larger, prospective studies.**

Improvements in BMI, HbA1c, LDL, and HDL after 52 weeks of APR treatment were greater in patients in higher risk categories at baseline



Includes patients who were treated with APR for 52 weeks and had both baseline and week 52 values. APR, apremilast; BMI, body mass index; CI, confidence interval; HbA1c, glycated hemoglobin; HDL, high-density lipoprotein; LDL, low-density lipoprotein.

Disclosures and Funding Statement

PJM: AbbVie, Amgen, Bristol Myers Squibb, Eli Lilly, Galapagos, Gilead, Inmagene, Janssen, Novartis, Pfizer, Sun, and UCB – grant/research support and consultant; Aclaris, Boehringer Ingelheim, GlaxoSmithKline, and MoonLake – consultant; AbbVie, Amgen, Eli Lilly, Janssen, Novartis, Pfizer, and UCB – speakers bureau. DDG: AbbVie, Amgen, Bristol Myers Squibb, Celgene, Eli Lilly, Galapagos, Gilead, Janssen, Novartis, Pfizer, and UCB – grant/research support or consulting fees. IBM: AbbVie, Amgen, Bristol Myers Squibb, Causeway, Dvelo, Lilly, MoonLake, Novartis, Pfizer, and UCB – honoraria or research support. S Chen, S Colgan, YK, LT: Amgen Inc. – employees and stockholders. NNM: Amgen, Eli Lilly, and Leo Pharm – consultant; AbbVie, Celgene, Janssen Pharmaceuticals, and Novartis – investigator.

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References: 1. Kamtchekor A and Ogdie A. *Rheumatol Ther*. 2020;7:447-456. 2. Dalbeth N, et al. *Rheumatology (Oxford)*. 2014;53(2):346-352. 3. Wu C and Rajagopalan S. *Obes Rev*. 2016;17:429-441. 4. Puig L, et al. *J Am Acad Dermatol*. 2018;79:AB151. 5. Gelfand JM, et al. *JAMA Dermatol*. 2022;158:1384-1685. 6. Otezla [summary of product characteristics]. Breda, The Netherlands: Amgen Europe B.V.; 2020. 7. Kavanaugh A, et al. *J Rheumatol*. 2015;42:479-488. 8. Cutolo M, et al. *J Rheumatol*. 2016;43:1724-1734. 9. Edwards CJ, et al. *Ann Rheum Dis*. 2016;75:1065-1073. 10. Wells AF, et al. *Rheumatology (Oxford)*. 2016;57:1253-1263. 11. Nash P, et al. *Ann Rheum Dis*. 2016;77:690-698.

Many patients shifted to healthier HbA1c, LDL, and HDL categories after 52 weeks of APR treatment

BMI Categories at Baseline*	BMI Categories at Week 52*			
	Obese	Overweight	Normal	
Normal (n = 124)	0.0%	10.5%	89.5%	Patients with ≥1 BMI category improvement
Overweight (n = 204)	7.8%	79.9%	12.3%	Patients with no change in BMI category
Obese (n = 267)	91.0%	9.0%	0.0%	Patients with ≥1 BMI category worsening

*Normal: <25 kg/m²; overweight: 25–<30 kg/m²; obese: ≥30 kg/m². BMI, body mass index.

HbA1c Categories at Baseline*	HbA1c Categories at Week 52*			
	Diabetes	Pre-diabetes	Normal	
Normal (n = 231)	0.4%	2.6%	97.0%	Patients with ≥1 HbA1c category improvement
Pre-diabetes (n = 119)	5.0%	44.5%	50.4%	Patients with no change in HbA1c category
Diabetes (n = 25)	56.0%	40.0%	4.0%	Patients with ≥1 HbA1c category worsening

*Normal: <5.7%; pre-diabetes: ≥5.7–<6.5%; diabetes: ≥6.5%. HbA1c, glycated hemoglobin.

LDL Categories at Baseline*	LDL Categories at Week 52*			
	High	Borderline	Normal	
Normal (n = 322)	2.2%	12.7%	85.1%	Patients with ≥1 LDL category improvement
Borderline (n = 128)	12.5%	49.2%	38.3%	Patients with no change in LDL category
High (n = 65)	47.7%	32.3%	20.0%	Patients with ≥1 LDL category worsening

*Normal: ≤129 mg/dL; borderline: >129–<160 mg/dL; high: ≥160 mg/dL. LDL, low-density lipoprotein.

HDL Categories at Baseline*	HDL Categories at Week 52*			
	Low	Borderline	Normal	
Normal (n = 165)	0.6%	18.2%	81.2%	Patients with ≥1 HDL category improvement
Borderline (n = 266)	7.1%	74.8%	18.0%	Patients with no change in HDL category
Low (n = 84)	54.8%	44.0%	1.2%	Patients with ≥1 HDL category worsening

*Normal: ≥60 mg/dL; borderline: ≥40–<60 mg/dL; low: <40 mg/dL. HDL, high-density lipoprotein.

Includes patients who were treated with APR for 52 weeks and had both baseline and week 52 values.

Presented at: ACR Convergence 2023; November 10–15, 2023; San Diego, California, USA

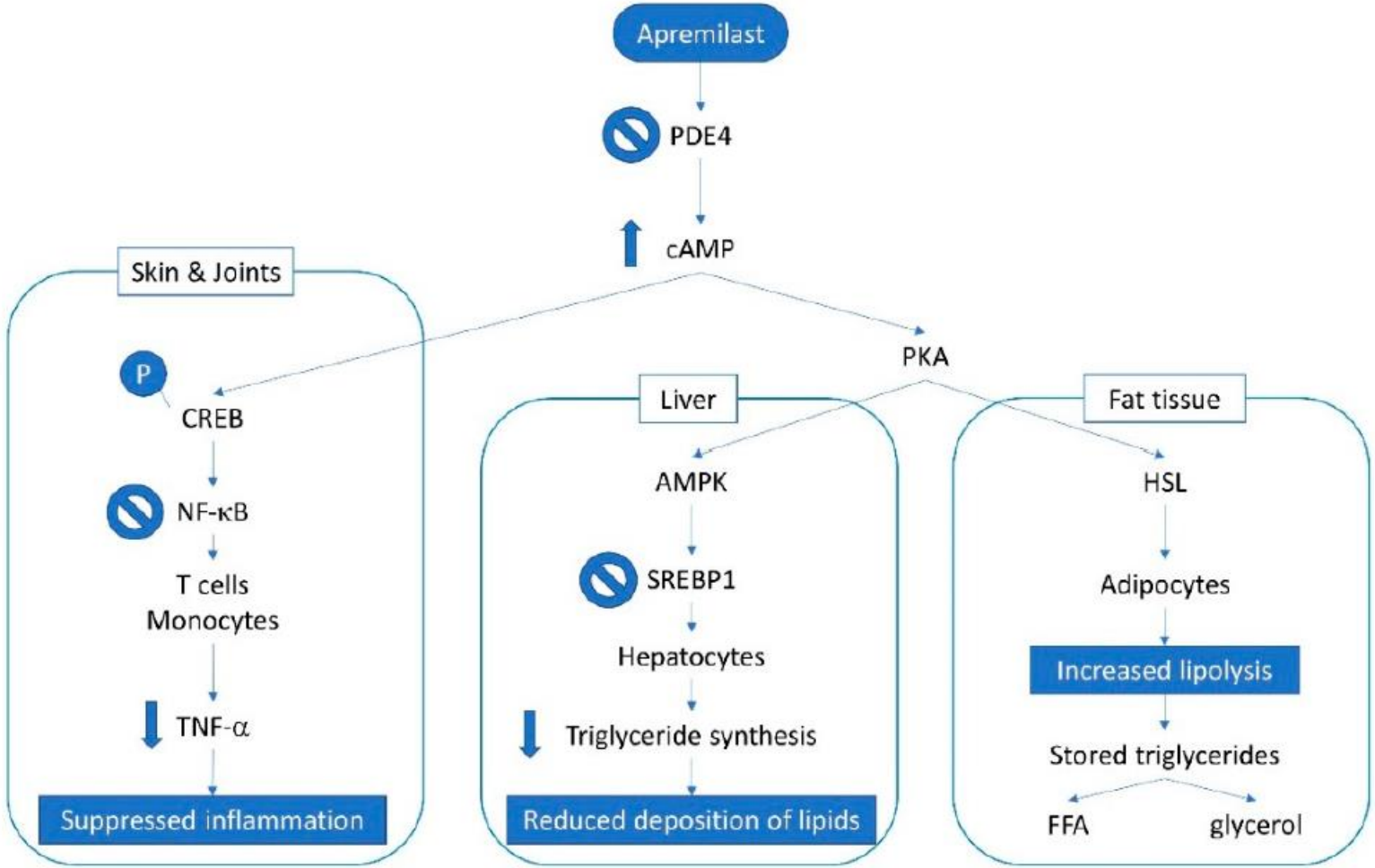
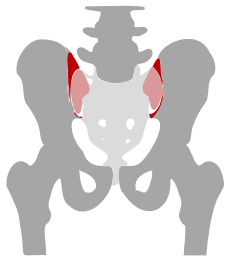


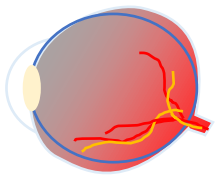
Figure 5. Overview of apremilast mechanism of action in psoriatic arthritis in different systems. Definitions: adenosine monophosphate kinase (AMPK); cyclic adenosine monophosphate (cAMP); cAMP response element-binding (protein) (CREB); free fatty acids (FFA); hormone-sensitive lipase (HSL); nuclear factor κB (NF-κB); phosphodiesterase 4 (PDE4); phosphokinase A (PKA); sterol regulatory element-binding protein 1 (SREBP1); tumor necrosis factor-alpha (TNF-α).

Gualtierotti R et al. J Clin Med, 2019; 8:398-408.

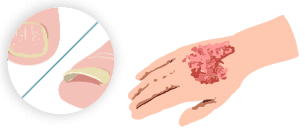
Key inflammatory cytokines are involved in SpA clinical features



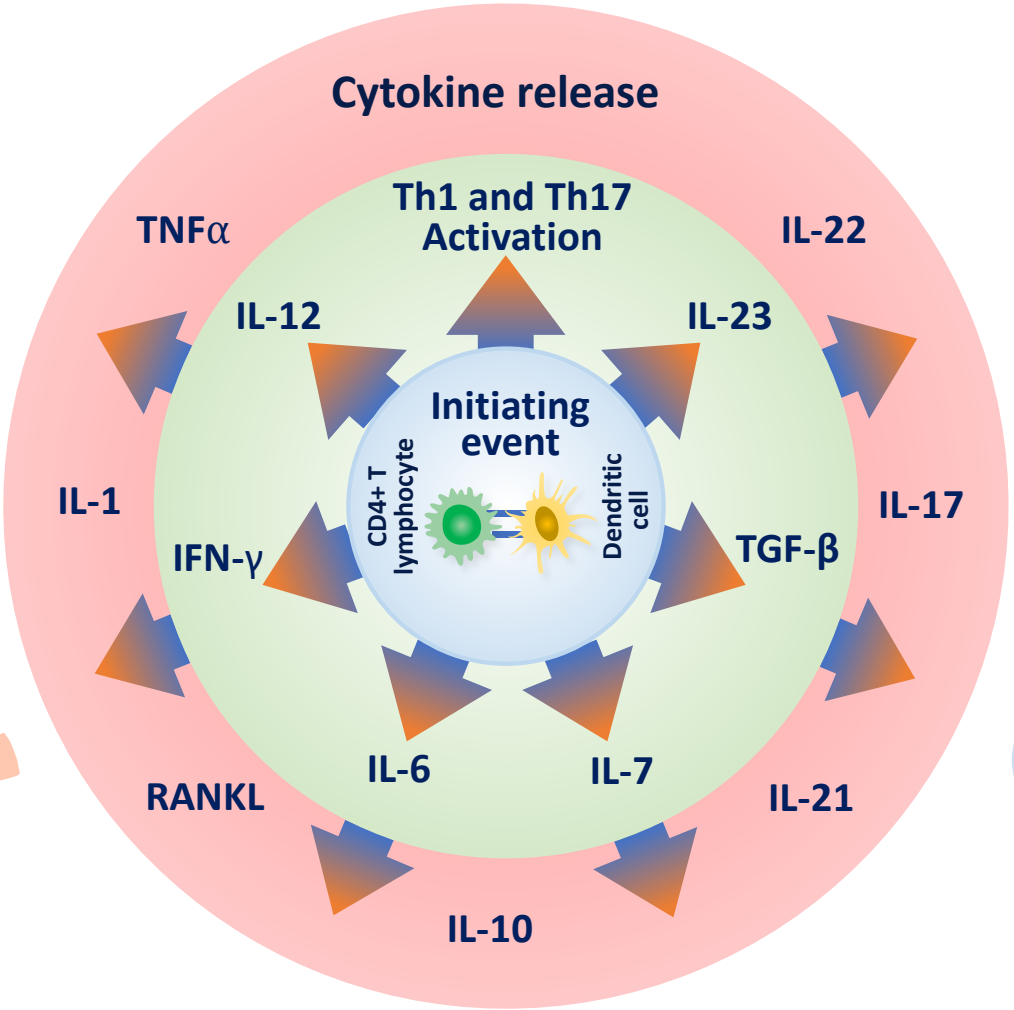
Syndesmophytes
Ankylosis

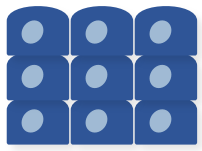


Uveitis

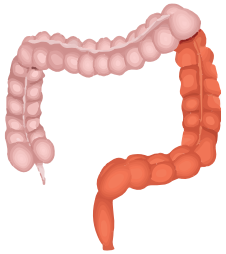


Skin and
nail psoriasis

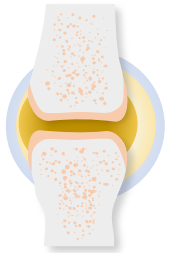




Osteoproliferation



Colitis

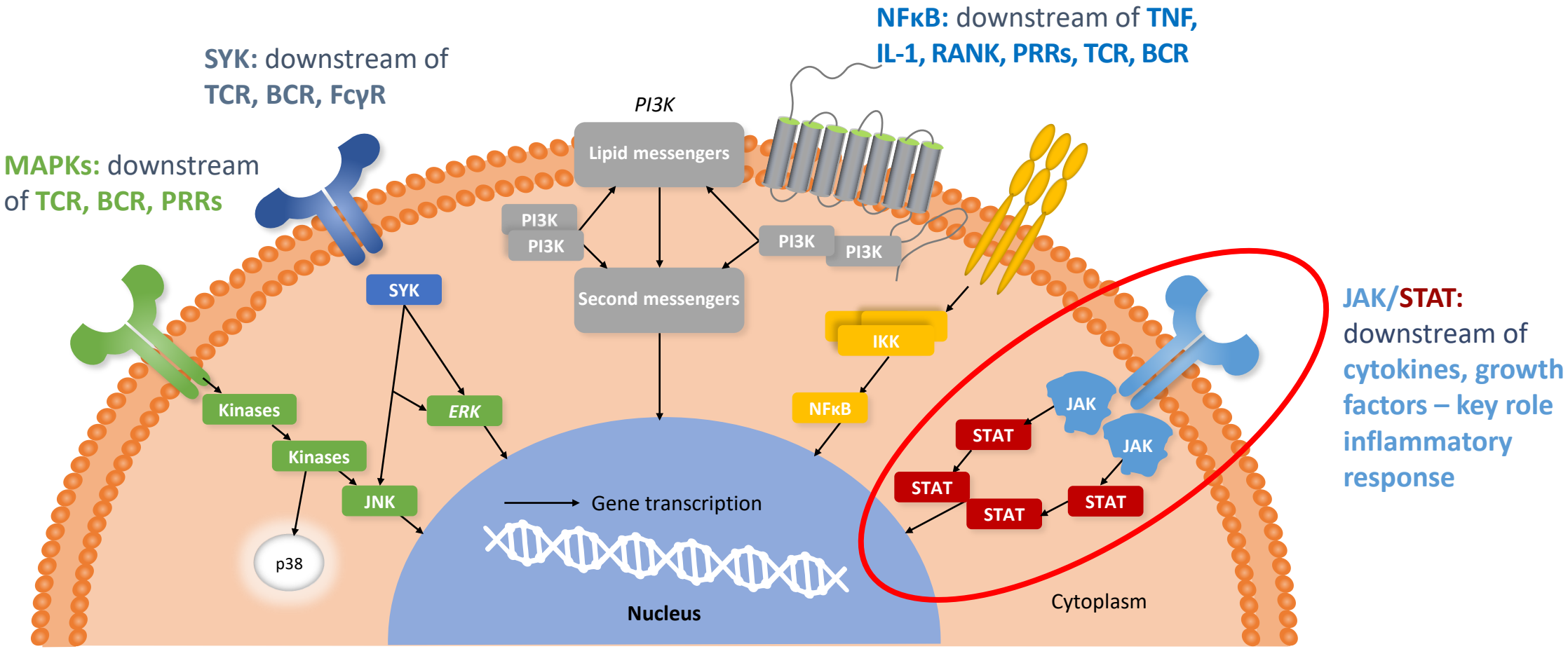


Tendonitis
Enthesitis
Osteitis
Dactylitis
Synovitis

EAM, extraarticular manifestation; IFN, interferon; IL, interleukin; RANKL, receptor activator of nuclear factor-kappa B ligand; SpA, spondyloarthritis; TGF, transforming growth factor; Th, T helper; TNF, tumor necrosis factor

Coates LC et al. Semin Arthritis Rheum 2016;46:291–304; Gonçalves RSG, Duarte ALBP. J Immunol Res 2019:745323; Lories RJ. Best Pract Res Clin Rheumatol 2018;32:331–341; Furst DE, Louie JS. Arthritis Res Ther 2019;21:135; Gravallese EM, Schett G. Nat Rev Rheumatol 2018;14:631–640; Boutet MA et al. Int J Mol Sci 2018;19(2). pii: E530; Ritchlin CT et al. N Engl J Med 2017;376:957–970; Veale DJ, Fearon U. Lancet 2018;391:2273–2284

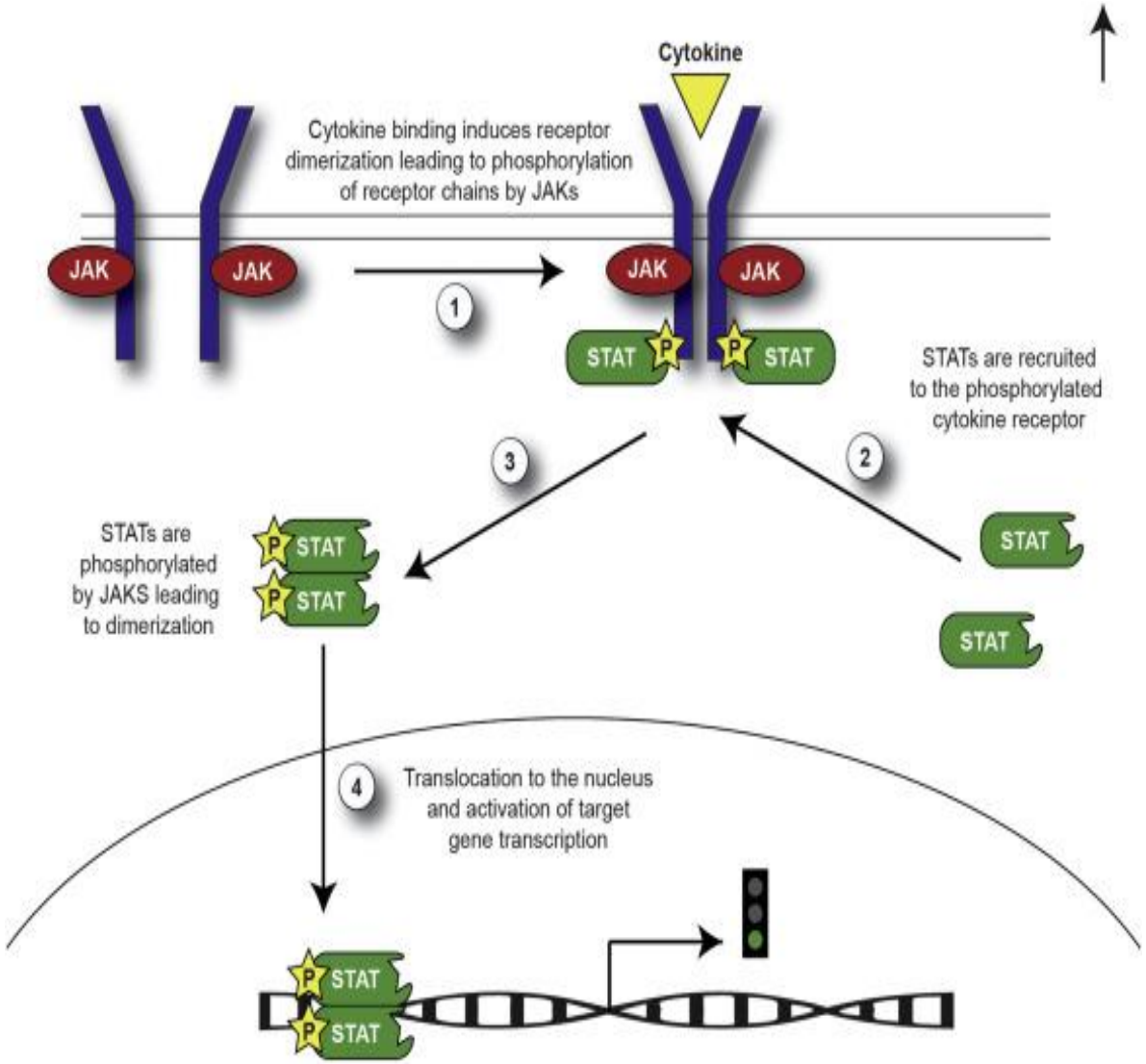
Cytokines signal through different intracellular pathways



BCR B-cell receptor; ERK extracellular signal-regulated kinase; FcγR Fc gamma receptor; IKK inhibitor of kappaB kinase; IL interleukin; JAK Janus kinase; JNK c-Jun N-terminal kinase; MAPK mitogen-activated protein kinase; NF-kB nuclear factor kappa beta; PI3K phosphatidylinositol-3 kinase; PRR pattern recognition receptor; RANK receptor activator of NF-kB; STAT signal transducer and activator of transcription; SYK spleen tyrosine kinase; TCR T-cell receptor; TNF tumor necrosis factor

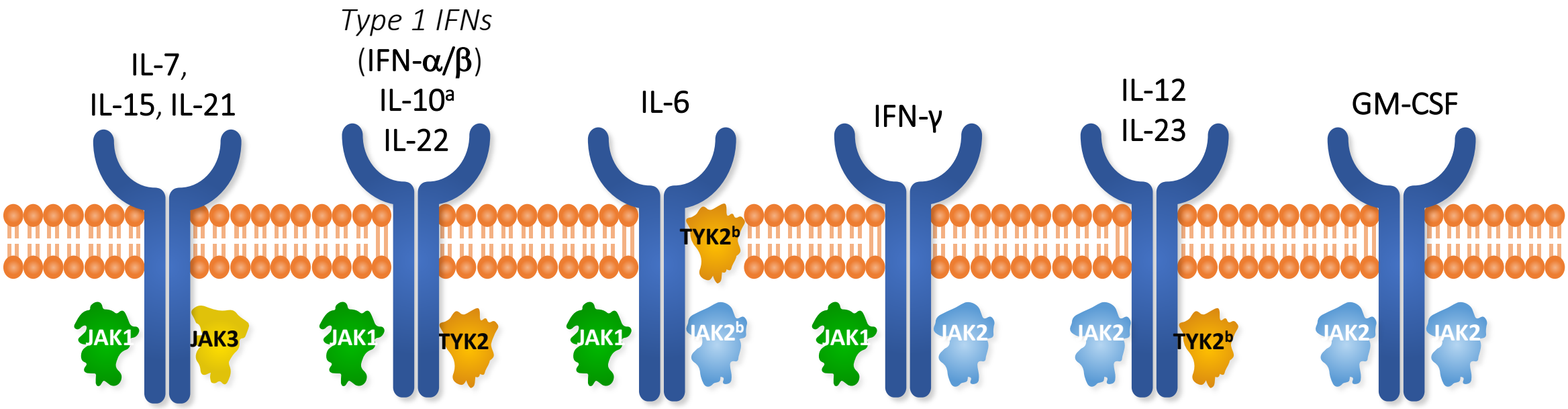
Diagram adapted from Cohen S. Int J Clin Rheumatol 2012;7:413–23
Clark JD et al. J Med Chem 2014;57:5023–5038; Ivashkiv LB, Donlin LT. Nat Rev Immunol 2014;14:36–49; Meier FM. Best Pract Res Clin Rheumatol 2014;28:605–24; Hayden M, Ghosh S. Semin Immunol 2014;26:253–66; Chen J, Chen ZJ. Curr Opin Immunol 2013; 25(1): 4-12; Brownlie RJ, Zamoyska R. Nat Rev Immunol. 2013; 13:257-269; Young RM, Staudt LM. Nat Rev Drug Disc. 2013; 12: 229-243

JAK/STAT pathway



JAK/TYK2 pairs[1,3,4]	Example cytokines[1,3,4]
TYK2 JAK1	• Type I IFN
TYK2 JAK2	• IL-12 • IL-23
JAK1 JAK2	• IL-6 • IFNγ
JAK1 JAK3	• IL-2 • IL-4 • IL-7 • IL-9 • IL-15 • IL-21
JAK2 JAK2	• EPO • TPO • GH • GM-CSF

Key cytokines and growth factor involved in SpA pathogenesis signal through JAK-STAT pathway

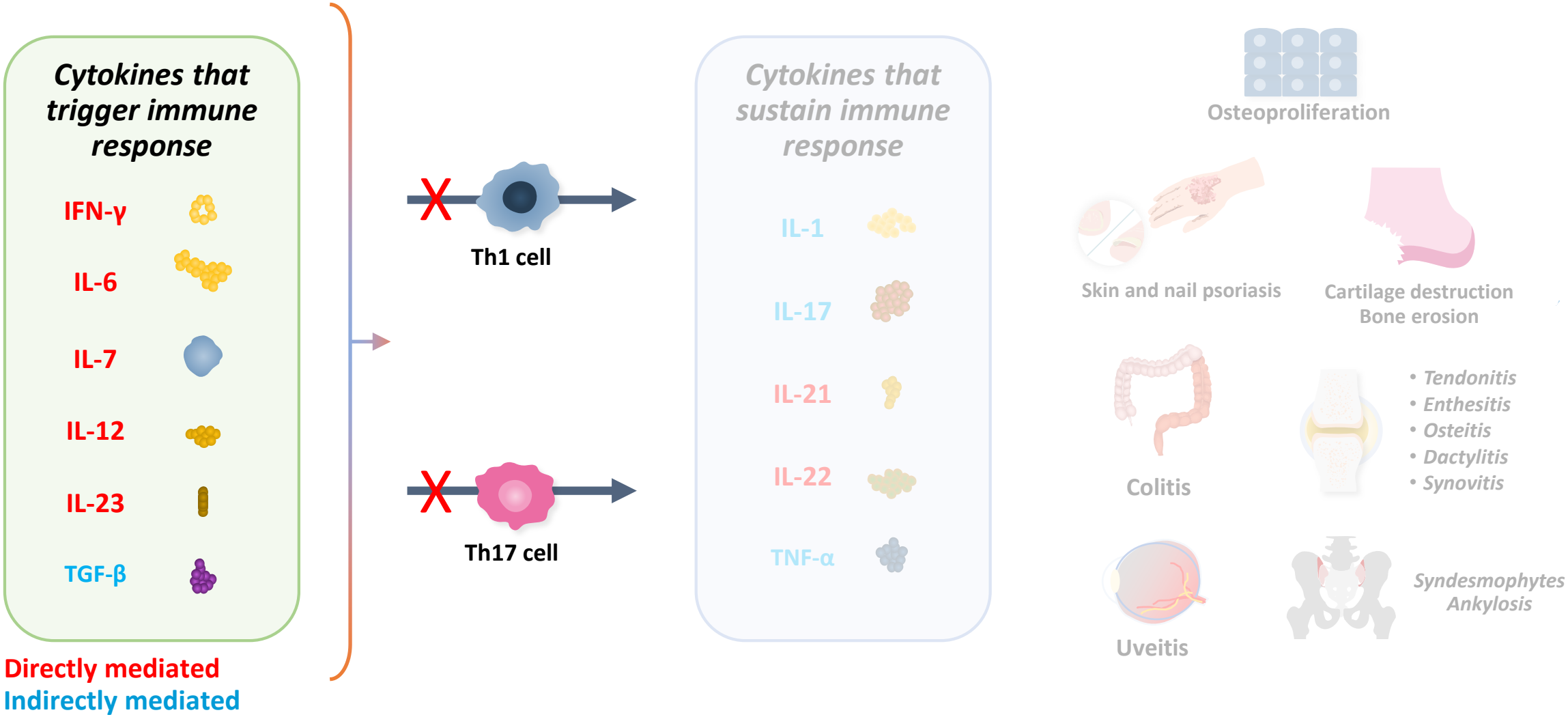


Each cytokine/growth factor **receptor** is associated with a **pair** of JAK family members, required for downstream signalling

[a]IL-10/IL-22 may have pro- or anti-inflammatory activities depending on the cellular environment and/or disease state [b]Type II cytokine receptors such as those for gp130 subunit sharing receptors for IL-6 and IL-11 as well as IL-10, IL-19, IL-20, and IL-22, mainly signal through JAK1, but also associate with JAK2 and TYK2
GM-CSF granulocyte macrophage colony-stimulating factor; IFN interferon; IL, interleukin; JAK, Janus kinase; SpA, spondyloarthritis;TYK2 tyrosine kinase 2

Figure adapted from: Clark JD et al. J Med Chem 2014;57:5023–5038; Liao HT et al. J Formos Med Assoc 2019;118(1 Pt 1):134–141; El Jammal T et al. Joint Bone Spine 2019 [Epub ahead of print]; Ghoreschi K et al. Immunol Rev 2009;228:273–287; Kerrigan SA, McInnes IB. Curr Rheumatol Rep 2018;20:83; Sanjabi S et al. Curr Opin Pharmacol 2009;9:447–453

Targeting the JAK-STAT pathway directly and indirectly inhibits the pathogenic immune response in SpA



Coates LC et al. Semin Arthritis Rheum 2016;46:291–304; Gonçalves RSG, Duarte ALBP. J Immunol Res 2019:745323; Lories RJ. Best Pract Res Clin Rheumatol. 2018;32:331–341; Furst DE, Louie JS. Arthritis Res Ther 2019;21:135; Gravallese EM, Schett G. Nat Rev Rheumatol 2018;14:631–640; Boutet MA et al. Int J Mol Sci 2018;19(2). pii: E530; Ritchlin CT et al. N Engl J Med 2017;376:957–970; Veale DJ, Fearon U. Lancet 2018;391:2273–2284; Horai R, Caspi RR. J Interferon Cytokine Res 2011;31:733–744; Van Praet L, et al. Nat Rev Rheumatol 2012;8:288–295; Schwartz DM et al. Nat Rev Rheumatol 2016;12:25–36; El Jammal T et al. Joint Bone Spine 2019

AGENZIA ITALIANA DEL FARMACO

DETERMINA 9 maggio 2022

Regime di rimborsabilita' e prezzo, a seguito di nuove indicazioni terapeutiche, (22A02915) (GU Serie Generale n.114 del 17-05-2022)

Le nuove indicazioni terapeutiche del medicinale [redacted] (upadacitinib):

«Artrite psoriasica

'[redacted] e' indicato nel trattamento dell'artrite psoriasica attiva nei pazienti adulti che hanno avuto una risposta inadeguata o che sono intolleranti ad uno o piu' DMARD.

'[redacted] puo' essere somministrato in monoterapia o in associazione con metotrexato».

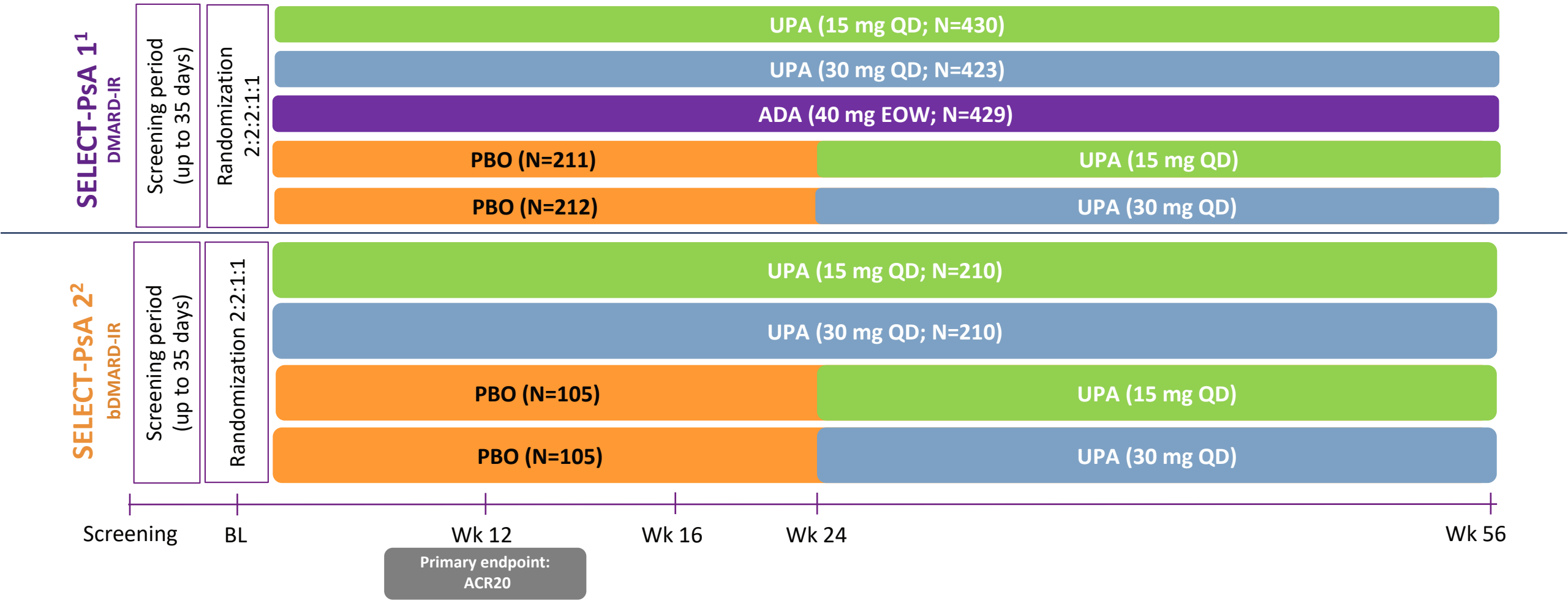
Posologia

Artrite reumatoide, artrite psoriasica e spondiloartrite assiale
La dose raccomandata di upadacitinib è di 15 mg una volta al giorno.

https://www.gazzettaufficiale.it/atto/serie_generale/caricaDettaglioAtto/originario?atto.dataPubblicazioneGazzetta=2022-05-17&atto.codiceRedazionale=22A02915&elenco30giorni=true

AIFA - Rinvoq® RCP

SELECT-PsA 1 and 2
Study design



All subjects will receive X-rays of hands and feet at screening, Week 24, Week 56, Week 104 and Week 152/PD. At Week 16, rescue therapy was offered to subjects classified as non-responders (defined as not achieving at least 20% improvement in tender joint count and swollen joint count at both Week 12 and Week 16). At Week 24, all PBO subjects will switch to UPA 15 mg QD or 30 mg QD (1:1 ratio) regardless of response.

ACR20, American College of Rheumatology 20% improvement score; ADA, adalimumab; b, biologic; BL, baseline; DMARD, disease-modifying anti-rheumatic drug; EOW, every other week; IR, inadequate response; PD, progressive disease; PsA, psoriatic arthritis; QD, once daily; UPA, upadacitinib; Wk, week.

1. McInnes I et al. Ann Rheum Dis 2020;79(Suppl 1):12;
2. Genovese MC et al. Ann Rheum Dis 2020;79(Suppl 1):139.

SELECT-PsA 1

Key inclusion and exclusion criteria

Inclusion criteria

- ≥18 years old at screening
- Clinical diagnosis of PsA with symptom onset >6 months prior to screening and fulfillment of the CASPAR criteria
- Active disease at baseline defined as ≥3 tender joints and ≥3 swollen joints
- Presence at screening of either ≥1 erosion on x-ray as determined by central imaging review or hs-CRP >ULN
- Diagnosis of active plaque psoriasis or documented history of plaque psoriasis
- Inadequate response or intolerance to treatment with at least one non-biologic DMARD*
- On ≤2 non-biologic DMARDs

Exclusion criteria

- Prior exposure to any JAK inhibitor
- Prior exposure to any bDMARD

*Lack of efficacy after ≥12 weeks of therapy; intolerance or contraindication as defined by investigator.
CRP, C-reactive protein; b, biologic; DMARD, disease-modifying anti-rheumatic drug; CASPAR, ClASsification criteria for Psoriatic ARthritis; JAK, Janus kinase; PsA, psoriatic arthritis; ULN, upper limits of normal.

McInnes I et al. Ann Rheum Dis 2020;79(Suppl 1):12

SELECT-PsA 2

Key inclusion and exclusion criteria

Inclusion criteria

- ≥18 years old at screening
- Clinical diagnosis of PsA with symptom onset at least 6 months prior to screening and fulfillment of the CASPAR criteria
- Active disease at baseline defined as ≥3 tender joints and ≥3 swollen joints
- Diagnosis of active plaque psoriasis or documented history of plaque psoriasis
- Inadequate response or intolerance to treatment with at least 1 bDMARD
- On ≤2 non-biologic DMARDs

Exclusion criteria

- Prior exposure to any JAK inhibitor

b, biologic; DMARD, disease-modifying anti-rheumatic drug; CASPAR, ClASsification criteria for Psoriatic ARthritis; JAK, Janus kinase; PsA, psoriatic arthritis.

Genovese MC et al. Ann Rheum Dis 2020;79(Suppl 1):139.

SELECT-PsA 1 and 2

Baseline demographic and disease characteristics

SELECT-PsA 1

DMARD-IR

Mean (SD) or n (%)	Placebo N=423	UPA 15 mg QD N=429*	UPA 30 mg QD N=423	ADA 40 mg EOW N=429
Female	211 (50%)	238 (56%)	236 (56%)	222 (52%)
Age, yrs	50.4 (12.21)	51.6 (12.19)	49.9 (12.41)	51.4 (12.04)
Duration of PsA symptoms, yrs	9.3 (8.58)	9.2 (8.63)	9.3 (8.28)	9.1 (8.78)
TJC68	20.0 (14.3)	20.4 (14.7)	19.4 (13.3)	20.1 (13.8)
SJC66	11.0 (8.2)	11.6 (9.3)	10.6 (7.1)	11.6 (8.8)
hsCRP >ULN†	324 (76.6%)	324 (75.5%)	324 (76.6%)	308 (71.8%)
HAQ-DI	1.12 (0.6)	1.15 (0.7)	1.09 (0.6)	1.12 (6.3)

SELECT-PsA 2

bDMARD-IR

Placebo N=212	UPA 15 mg QD N=211	UPA 30 mg QD N=218
120 (57%)	113 (54%)	115 (53%)
54.1 (11.5)	53.0 (12.0)	53.0 (11.9)
14.6 (11.7)	12.2 (8.8)	13.3 (10.8)
25.3 (17.6)	24.9 (17.3)	24.2 (15.9)
12.0 (8.9)	11.3 (8.2)	12.9 (9.4)
121 (57.1%)	126 (59.7%)	128 (58.7%)
1.23 (0.7)	1.10 (0.6)	1.19 (0.7)

*430 randomized, 429 received double-blind study treatment. †ULN = 2.87 mg/L for hsCRP.
ADA, adalimumab; b, biologic; DMARD, disease-modifying anti-rheumatic drug; EOW, every other week; HAQ-DI, Health Assessment Questionnaire Disability index; hsCRP, high-sensitivity C-reactive protein; IR, inadequate response; PsA, psoriatic arthritis; QD, once daily; SD, standard deviation; SJC66, swollen joint count 66;
TJC68, tender joint count 68; ULN, upper limit of normal; UPA, upadacitinib; yrs, years.

1. McInnes I et al. Ann Rheum Dis 2020;79(Suppl 1):12;
2. Genovese MC et al. Ann Rheum Dis 2020;79(Suppl 1):139.

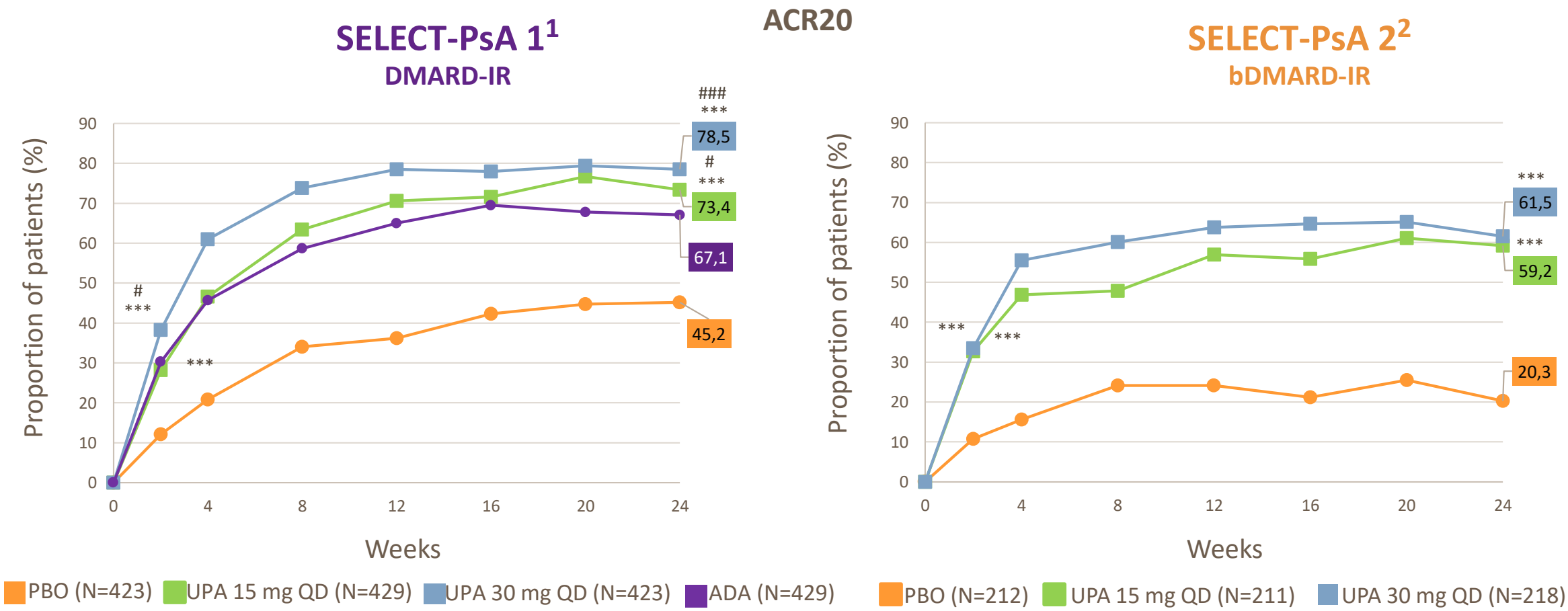
SELECT-PsA 1 and 2
Baseline disease characteristics

	SELECT-PsA 1 DMARD-IR				SELECT-PsA 2 bDMARD-IR		
Mean (SD) or n (%)	**Placebo N=423**	**UPA 15 mg QD N=429***	**UPA 30 mg QD N=423**	**ADA 40 mg EOW N=429**	**Placebo N=212**	**UPA 15 mg QD N=211**	**UPA 30 mg QD N=218**
≥3% BSA-Ps	211 (49.9%)	214 (49.9%)	210 (49.6%)	211 (49.2%)	131 (62%)	130 (62%)	131 (60%)
PASI (for baseline BSA-Ps ≥3%)	11.21 (11.4)	9.78 (10.0)	9.45 (8.8)	9.42 (8.5)	11.7 (11.4)	10.1 (9.2)	8.9 (9.1)
Presence of enthesitis (LEI>0)	241 (57.0%)	270 (62.9%)	267 (63.1%)	265 (61.8%)	173 (82%)	173 (82%)	181 (83%)
Presence of dactylitis (LDI>0)	126 (29.8%)	136 (31.7%)	127 (30.0%)	127 (29.6%)	64 (30%)	55 (26%)	50 (23%)

*430 randomized, 429 received double-blind study treatment.
ADA, adalimumab; b, biologic; BSA-Ps, body surface area psoriasis; DMARD, disease-modifying anti-rheumatic drug; EOW, every other week; IR, inadequate response; LDI, Leeds Dactylitis Index; LEI, Leeds Enthesitis Index; PASI, Psoriasis Area Severity Index; PsA, psoriatic arthritis; QD, once daily; SD, standard deviation; ULN, upper limit of normal; UPA, upadacitinib.

1. McInnes I et al. Ann Rheum Dis 2020;79(Suppl 1):12;
2. Genovese MC et al. Ann Rheum Dis 2020;79(Suppl 1):139.

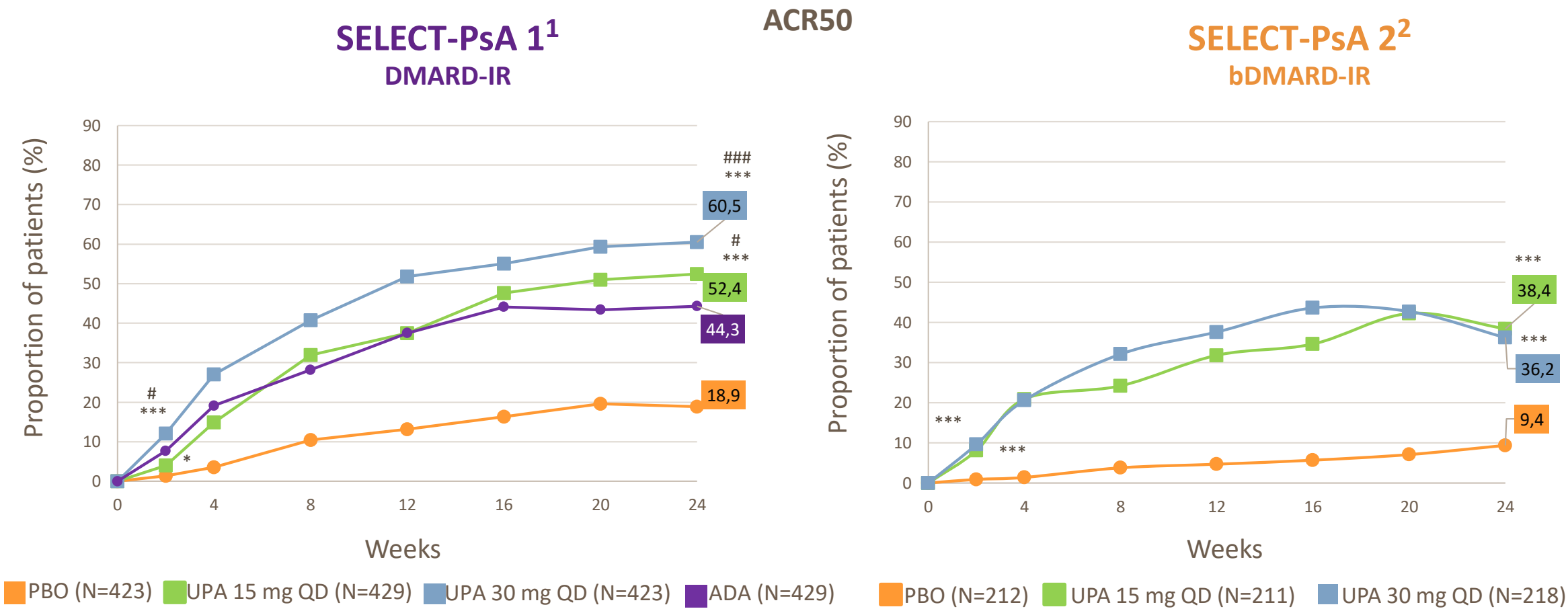
SELECT-PsA 1 and 2
ACR20 responses over time through Week 24 (NRI)



***p≤0.001 for UPA vs PBO; #p≤0.05, ###p≤0.001 for UPA vs ADA. . [ ]Statistically significant in the multiplicity-controlled analysis.
ACR20, American College of Rheumatology 20% improvement score; ADA, adalimumab; b, biologic; DMARD; disease-modifying anti-rheumatic drug; IR, inadequate response; NRI, non-responder imputation; PBO, placebo; PsA, psoriatic arthritis; QD, once daily; UPA, upadacitinib.

1. McInnes I et al. Ann Rheum Dis 2020;79(Suppl 1):12;
2. Genovese MC et al. Ann Rheum Dis 2020;79(Suppl 1):139.

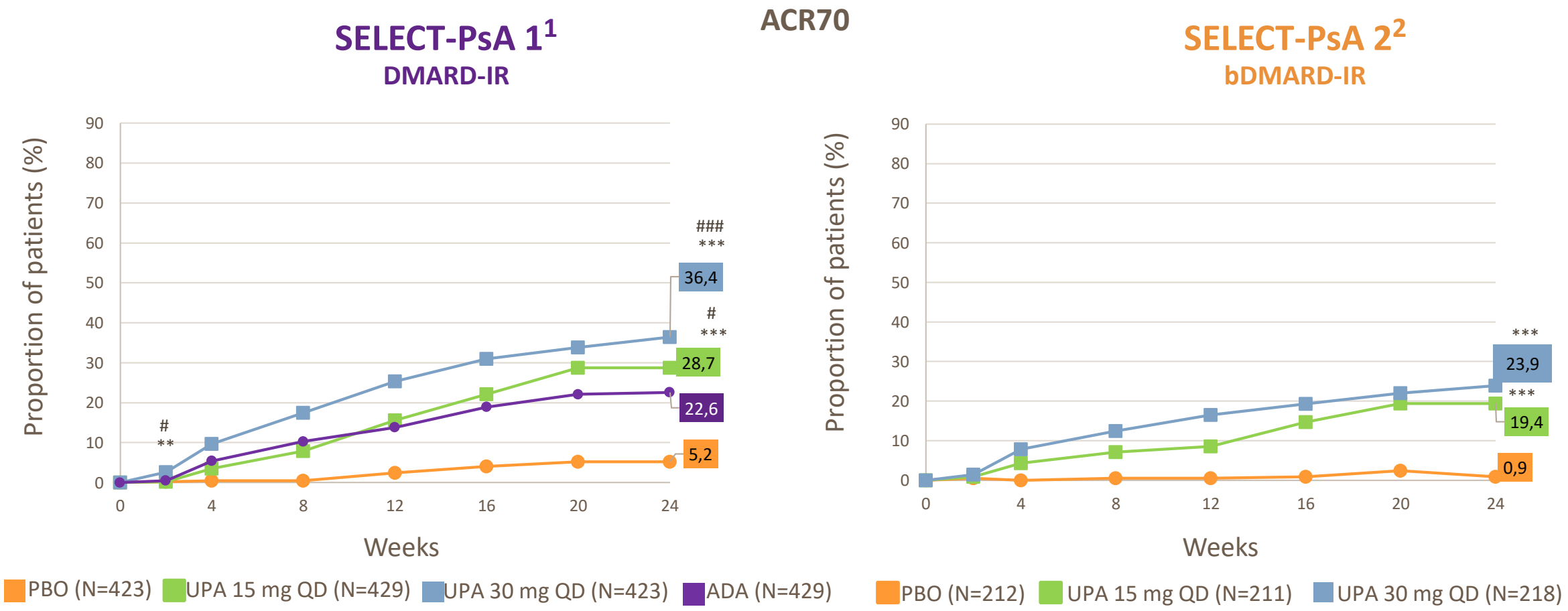
SELECT-PsA 1 and 2
ACR50 responses over time through Week 24 (NRI)



***p≤0.001 for UPA vs PBO; #p≤0.05, ###p≤0.001 for UPA vs ADA. . [ ]Statistically significant in the multiplicity-controlled analysis. ACR50, American College of Rheumatology 50% improvement score; ADA, adalimumab; b, biologic; DMARD; disease-modifying anti-rheumatic drug; IR, inadequate response; NRI, non-responder imputation; PBO, placebo; PsA, psoriatic arthritis; QD, once daily; UPA, upadacitinib.

1. McInnes I et al. Ann Rheum Dis 2020;79(Suppl 1):12;
2. Genovese MC et al. Ann Rheum Dis 2020;79(Suppl 1):139.

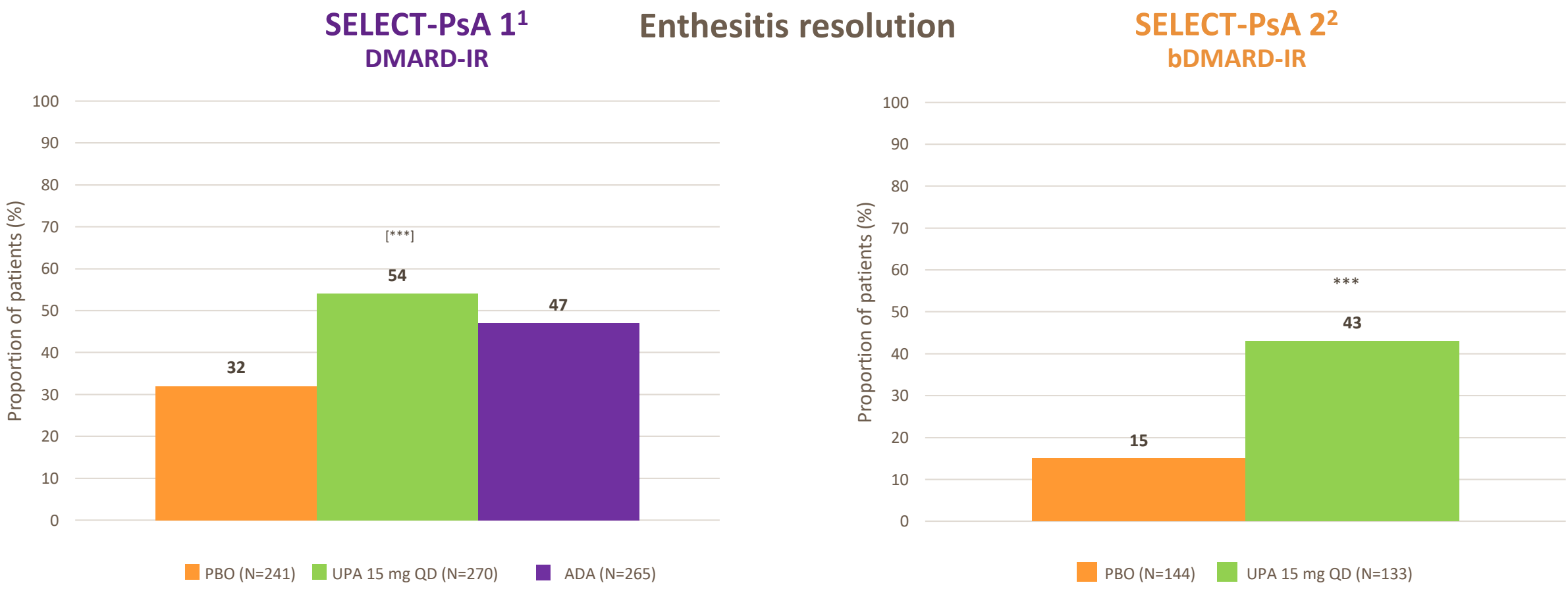
SELECT-PsA 1 and 2
ACR70 responses over time through Week 24 (NRI)



***p≤0.001 for UPA vs PBO; #p≤0.05; ###p≤0.001 for UPA vs ADA. . [ ]Statistically significant in the multiplicity-controlled analysis.
ACR70, American College of Rheumatology 70% improvement score; ADA, adalimumab; b, biologic; DMARD; disease-modifying anti-rheumatic drug; IR, inadequate response; NRI, non-responder imputation; PBO, placebo; PsA, psoriatic arthritis; QD, once daily; UPA, upadacitinib.

1. McInnes I et al. Ann Rheum Dis 2020;79(Suppl 1):12;
2. Genovese MC et al. Ann Rheum Dis 2020;79(Suppl 1):139.

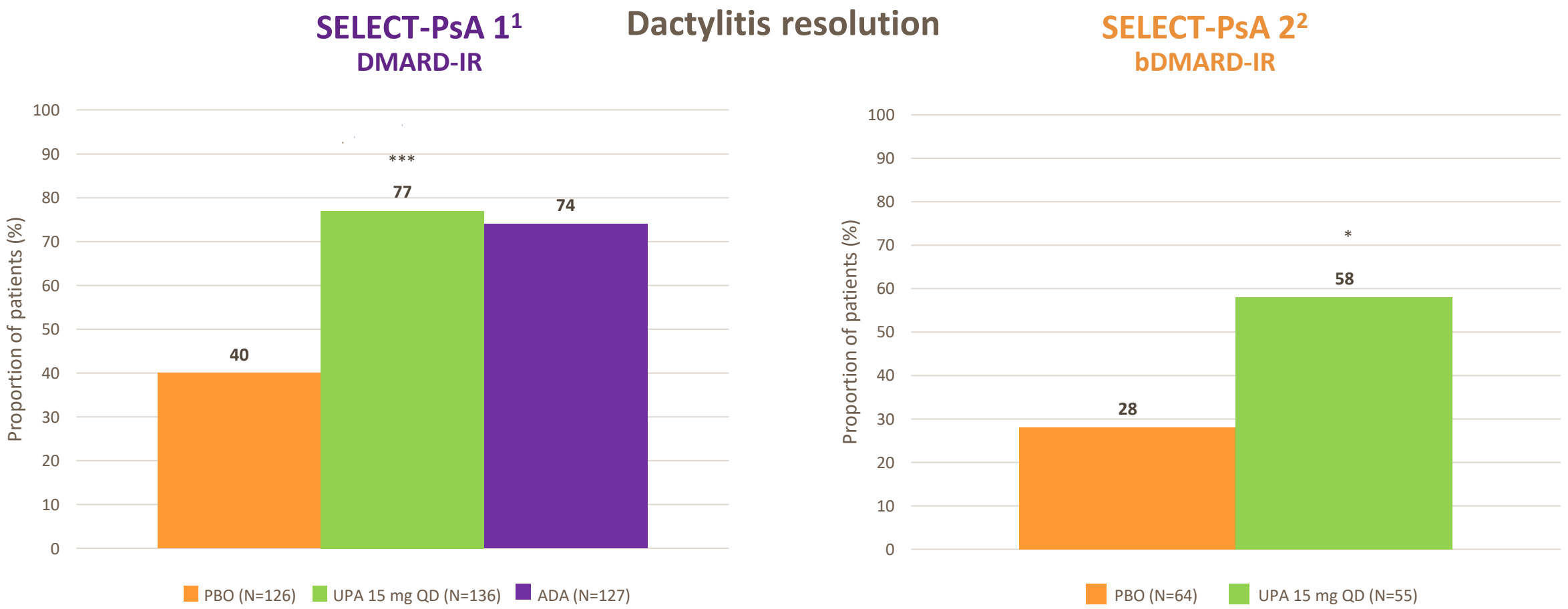
Enthesitis: SELECT-PsA 1 and 2 Resolution of enthesitis at Week 24[a] (NRI)



[a]For patients with enthesitis at baseline; resolution of enthesitis defined as LEI=0.
***p≤0.001 for UPA vs PBO. [ ] Statistically significant in the multiplicity-controlled analysis.
ADA, adalimumab; b, biologic; DMARD, disease-modifying anti-rheumatic drug; IR, inadequate response; LEI, Leeds Enthesitis Index; NRI, non-responder imputation; PBO, placebo; PsA, psoriatic arthritis; QD, once daily; UPA, upadacitinib.

1. McInnes I et al. Ann Rheum Dis 2020;79(Suppl 1):12;
2. Genovese MC et al. Ann Rheum Dis 2020;79(Suppl 1):139.

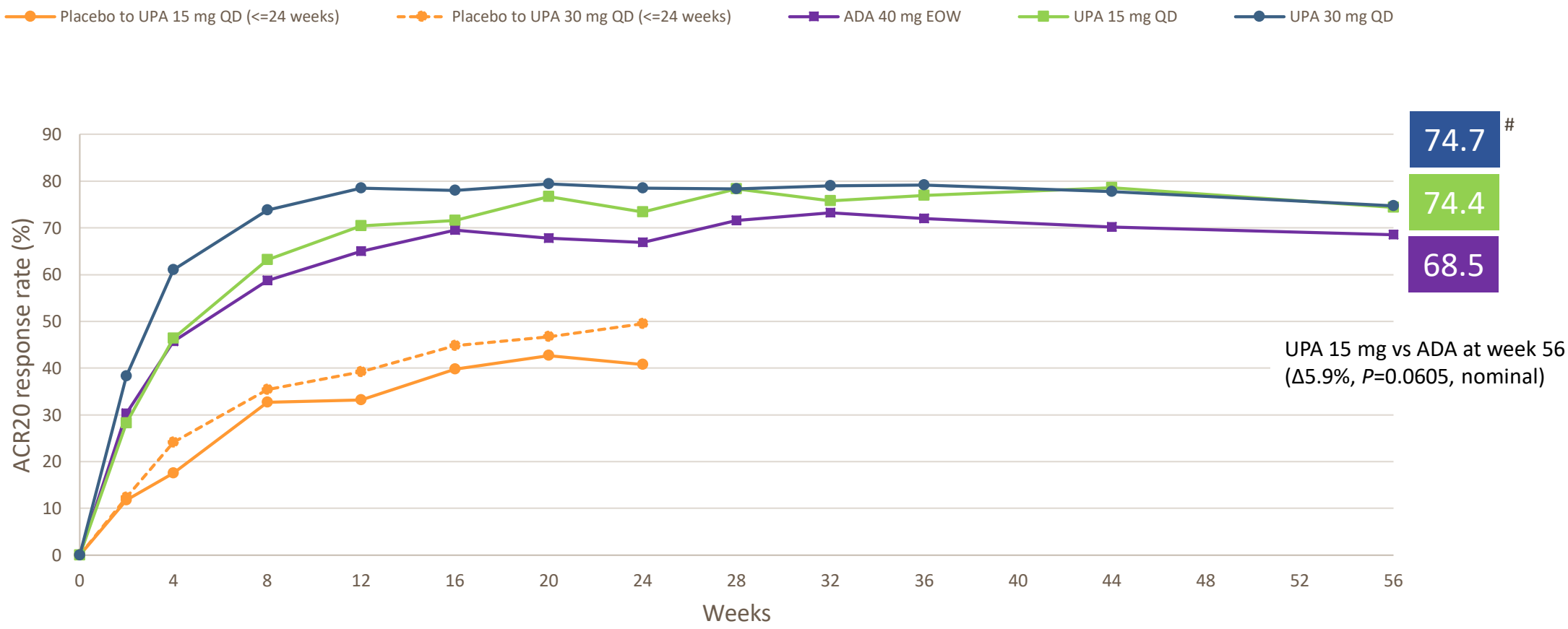
Dactylitis: SELECT-PsA 1 and 2 Resolution of dactylitis at Week 24[a] (NRI)



[a]For patients with dactylitis at baseline; resolution of dactylitis defined as LDI=0.
*p≤0.05, ***p≤0.001 for UPA vs PBO, non-multiplicity controlled in SELECT-PsA 1.
ADA, adalimumab; b, biologic; DMARD, disease-modifying anti-rheumatic drug; IR, inadequate response; NRI, non-responder imputation; LDI, Leeds Dactylitis Index; PBO, placebo; PsA, psoriatic arthritis; QD, once daily; UPA, upadacitinib.

1. McInnes I et al. Ann Rheum Dis 2020;79(Suppl 1):12;
2. Genovese MC et al. Ann Rheum Dis 2020;79(Suppl 1):139.

SELECT-PsA 1
ACR20 response through **Week 56** (NRI) – UPA 15 and 30 mg

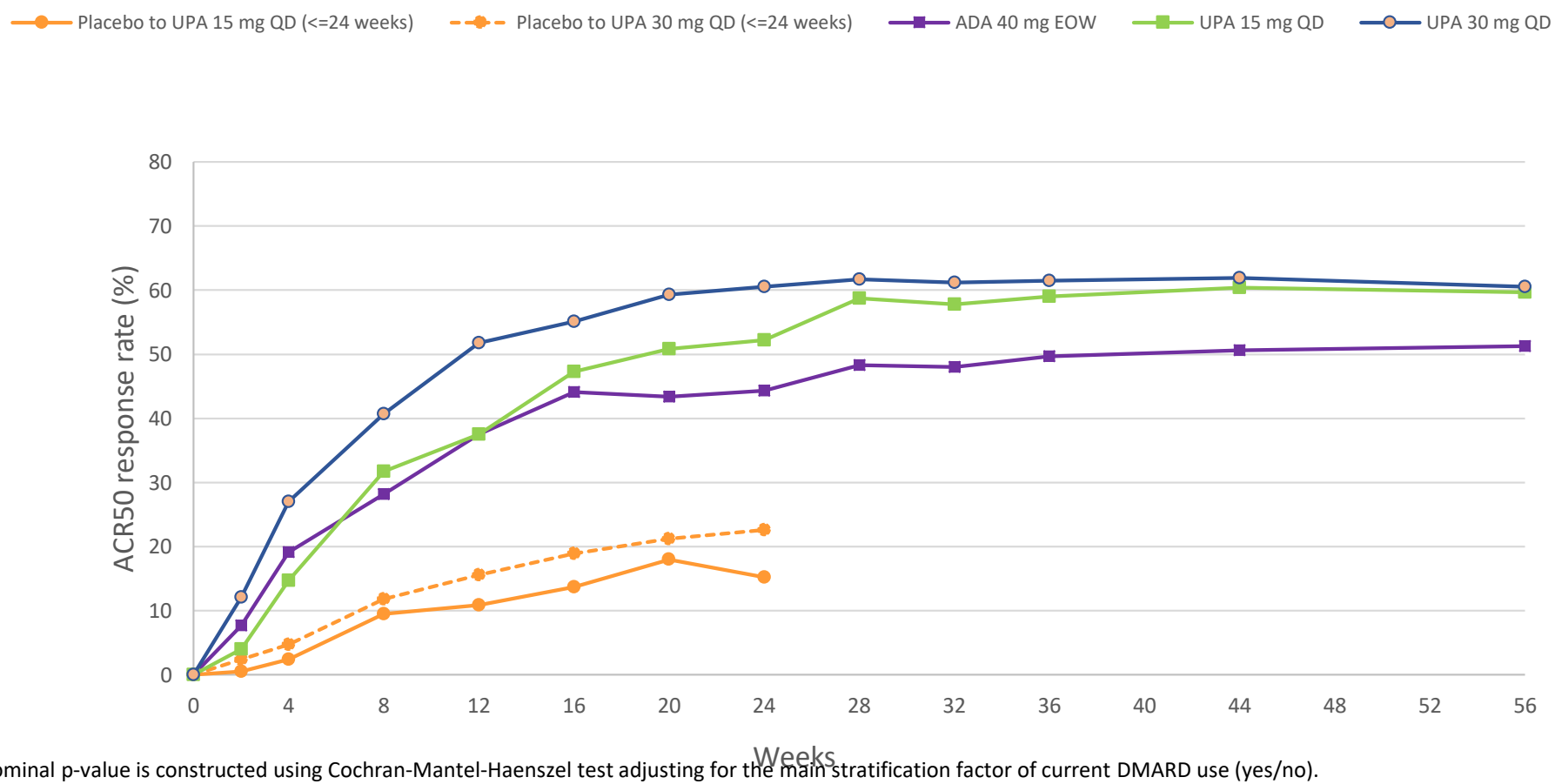


Nominal p-value is constructed using Cochran-Mantel-Haenszel test adjusting for the main stratification factor of current DMARD use (yes/no).
#p≤0.05 for UPA vs ADA . [ ]Statistically significant in the multiplicity-controlled analysis.
At Week 16, rescue therapy offered to subjects classified as non-responders (defined as not achieving ≥20% improvement in tender and swollen joint count at both Week 12 and Week 16).
At Week 36 patients could change or initiate background DMARD therapy.

ACR20, American College of Rheumatology 20% improvement score; ADA, adalimumab; DMARD, disease-modifying anti-rheumatic drug; EOW, every other week; IR, inadequate response; NRI, non-responder imputation; PBO, placebo; PsA, psoriatic arthritis; QD, once daily; UPA, upadacitinib.

McInnes IB, et al.. RMD Open. 2021 Oct;7(3):e001838.

SELECT-PsA 1
ACR50 response through **Week 56** (NRI) – UPA 15 and 30 mg



60.5 ##

59.7 #

51.3

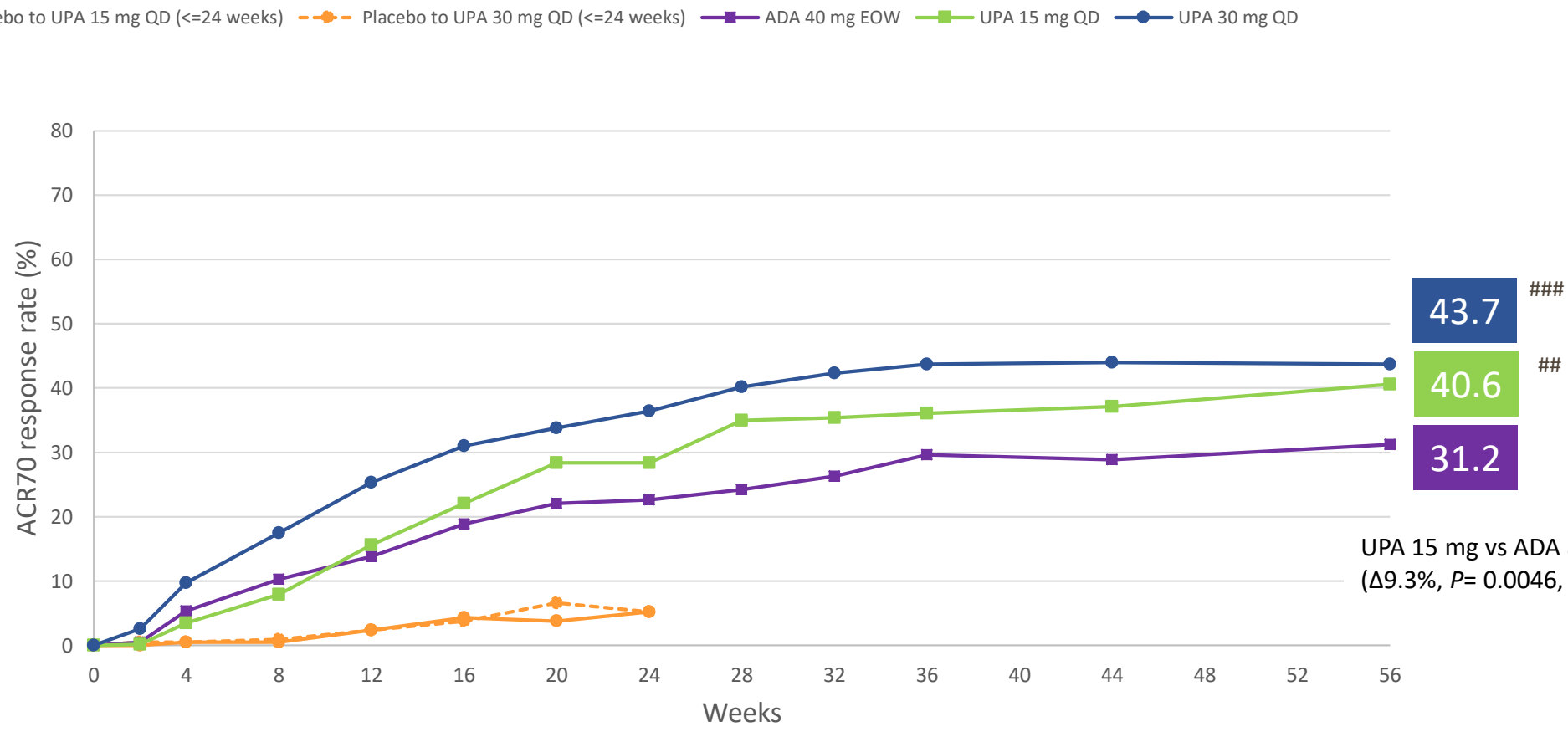
UPA 15 mg vs ADA at week 56
(Δ8.4%, *P*= 0.0142, nominal)

Nominal p-value is constructed using Cochran-Mantel-Haenszel test adjusting for the main stratification factor of current DMARD use (yes/no).
#p≤0.05, ##p ≤0.01 for UPA vs ADA . [ ]Statistically significant in the multiplicity-controlled analysis.
At Week 16, rescue therapy offered to subjects classified as non-responders (defined as not achieving ≥20% improvement in tender and swollen joint count at both Week 12 and Week 16).
At Week 36 patients could change or initiate background DMARD therapy..

ACR50, American College of Rheumatology 50% improvement score; ADA, adalimumab; DMARD, disease-modifying anti-rheumatic drug; EOW, every other week; IR, inadequate response; NRI, non-responder imputation; PBO, placebo; PsA, psoriatic arthritis; QD, once daily; UPA, upadacitinib.

McInnes IB, et al.. RMD Open. 2021 Oct;7(3):e001838.

SELECT-PsA 1
ACR70 response through **Week 56** (NRI) – UPA 15 and 30 mg



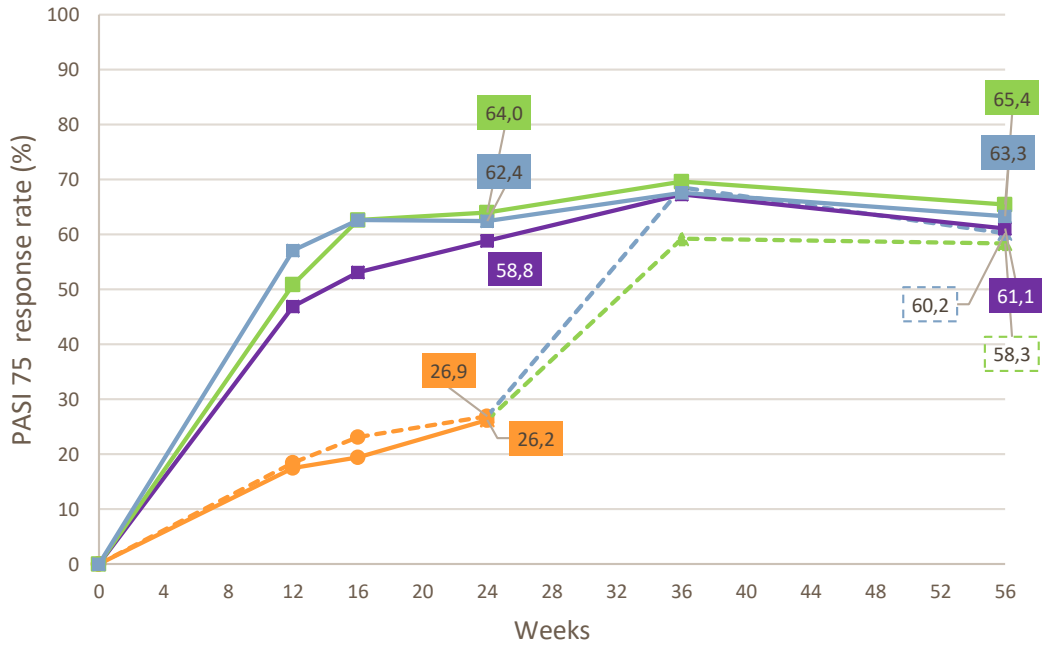
UPA 15 mg vs ADA at week 56
(Δ9.3%, *P*= 0.0046, nominal)

Nominal p-value is constructed using Cochran-Mantel-Haenszel test adjusting for the main stratification factor of current DMARD use (yes/no).
##p ≤0.01, ###p≤0.001 for UPA vs ADA . [ ]Statistically significant in the multiplicity-controlled analysis.
At Week 16, rescue therapy offered to subjects classified as non-responders (defined as not achieving ≥20% improvement in tender and swollen joint count at both Week 12 and Week 16).
At Week 36 patients could change or initiate background DMARD therapy.
ACR70, American College of Rheumatology 70% improvement score; ADA, adalimumab; DMARD, disease-modifying anti-rheumatic drug; EOW, every other week; IR, inadequate response; NRI, non-responder imputation; PBO, placebo; PsA, psoriatic arthritis; QD, once daily; UPA, upadacitinib.

McInnes IB, et al.. RMD Open. 2021 Oct;7(3):e001838.

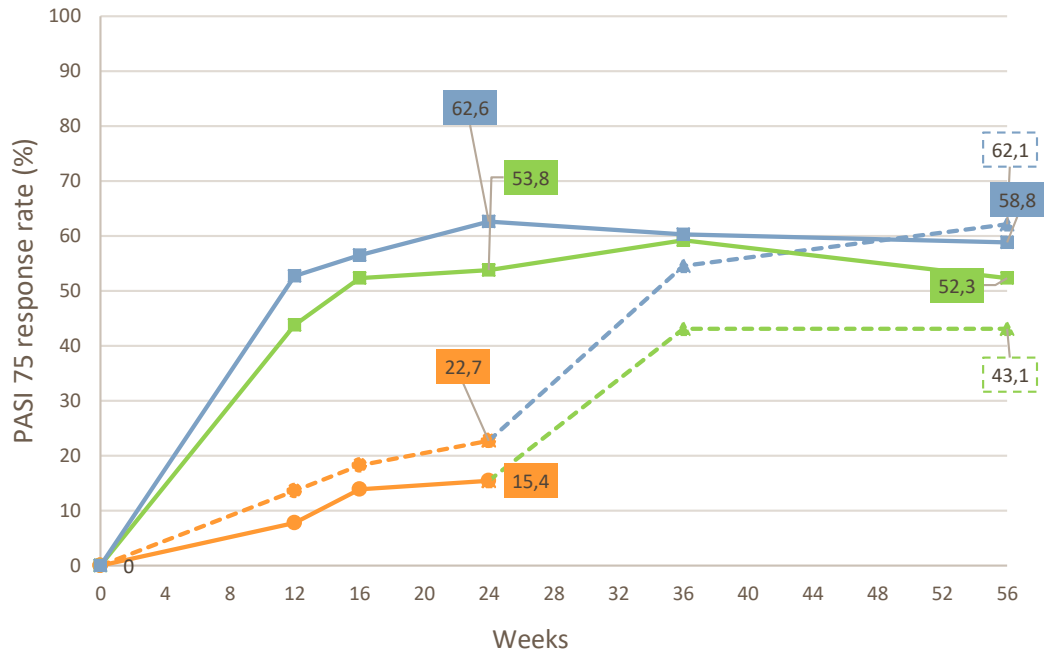
SELECT-PsA 1 and 2
PASI 75[a] response through Week 56 (NRI) – UPA 15 and 30 mg

SELECT-PsA 1 DMARD-IR



PBO* (→ UPA 15 mg QD; N=103)
PBO → UPA 15 mg QD (N=103)
UPA 15 mg QD (N=214)
ADA (N=211)
PBO* (→ UPA 30 mg QD; N=108)
PBO → UPA 30 mg QD (N=108)
UPA 30 mg QD (N=210)

SELECT-PsA 2 bDMARD-IR



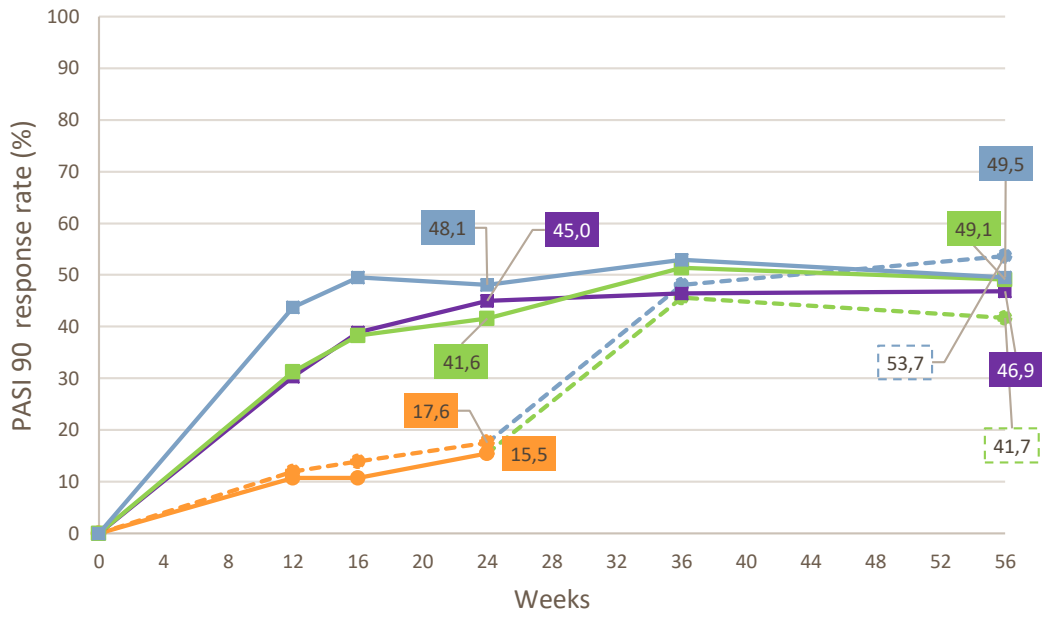
PBO* (→ UPA 15 mg QD; N=65)
PBO → UPA 15 mg QD (N=65)
UPA 15 mg QD (N=130)
PBO* (→ UPA 30 mg QD; N=66)
PBO → UPA 30 mg QD (N=66)
UPA 30 mg QD (N=131)

*Subjects could utilize any PsO therapies after Week 16, except for DMARDs unless qualified for rescue.
[a]For subjects with ≥3% BSA psoriasis at baseline. At Week 36 patients could change or initiate background DMARD therapy.
ADA, adalimumab; b, biologic; DMARD, disease-modifying anti-rheumatic drug; IR, inadequate response; PASI 75, Psoriasis Area Severity Index 75; PBO, placebo; NRI, non-responder imputation; PBO, placebo; PsA, psoriatic arthritis; PsO, psoriasis; QD, once daily; UPA, upadacitinib.

Mease PJ, et al. *Rheumatol Ther* 8, 903–919 (2021).
McInnes IB, et al. RMD Open 2021;7:e001838

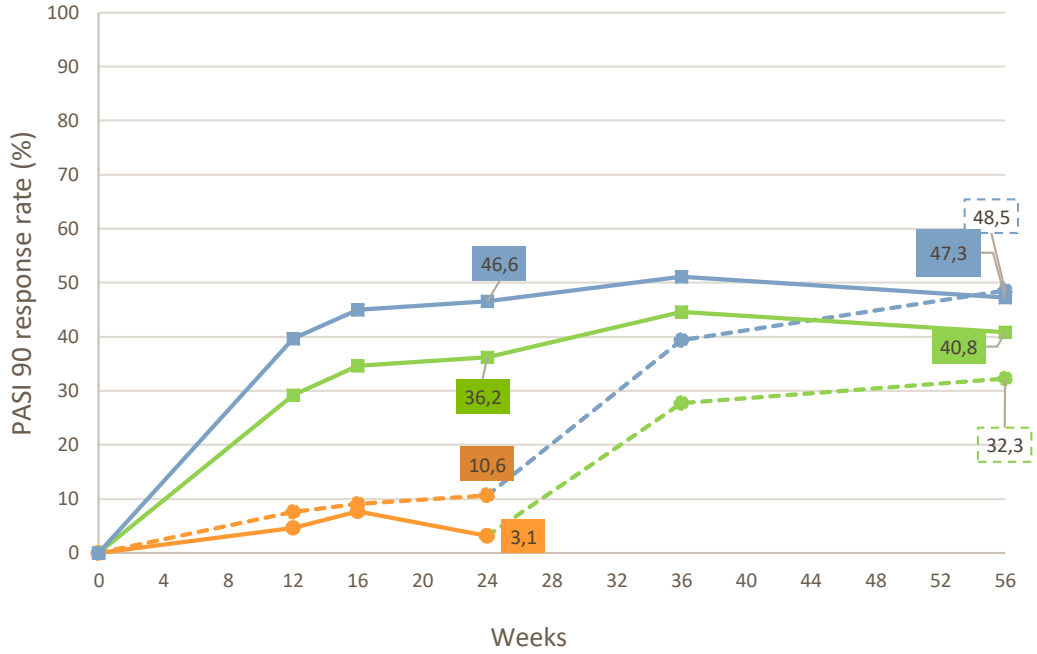
SELECT-PsA 1 and 2
PASI 90[a] response through Week 56 (NRI) – UPA 15 and 30 mg

SELECT-PsA 1 DMARD-IR



PBO* (→ UPA 15 mg QD; N=103)
PBO → UPA 15 mg QD (N=103)
UPA 15 mg QD (N=214)
ADA (N=211)
PBO* (→ UPA 30 mg QD; N=108)
PBO → UPA 30 mg QD (N=108)
UPA 30 mg QD (N=210)

SELECT-PsA 2 bDMARD-IR



PBO* (→ UPA 15 mg QD; N=65)
PBO → UPA 15 mg QD (N=65)
UPA 15 mg QD (N=130)
PBO* (→ UPA 30 mg QD; N=66)
PBO → UPA 30 mg QD (N=66)
UPA 30 mg QD (N=131)

*Subjects could utilize any PsO therapies after Week 16, except for DMARDs unless qualified for rescue.
[a]For subjects with ≥3% BSA psoriasis at baseline. At Week 36 patients could change or initiate background DMARD therapy.
ADA, adalimumab; b, biologic; DMARD, disease-modifying anti-rheumatic drug; IR, inadequate response; PASI 90, Psoriasis Area Severity Index 90; PBO, placebo; NRI, non-responder imputation; PBO, placebo; PsA, psoriatic arthritis; PsO, psoriasis; QD, once daily; UPA, upadacitinib.

Mease PJ, et al. *Rheumatol Ther* 8, 903–919 (2021).
McInnes IB, et al. RMD Open 2021;7:e001838

SELECT-PsA 1 and 2: Overview of treatment-emergent AEs through Week 24

	SELECT-PsA 1 (DMARD-IR)[1]			SELECT-PsA 2 (bDMARD-IR)[2]	
n (%)	PBO N=423	UPA 15 mg QD N=429	ADA 40 mg EOW N=429	PBO N=212	UPA 15 mg QD N=211
AEs	252 (59.6)	287 (66.9)	278 (64.8)	139 (65.6)	135 (64.0)
Serious AEs	13 (3.1)	14 (3.3)	16 (3.7)	4 (1.9)	12 (5.7)
AEs leading to discontinuation	13 (3.1)	13 (3.0)	22 (5.1)	11 (5.2)	15 (7.1)
Severe AEs	16 (3.8)	21 (4.9)	27 (6.3)	8 (3.8)	13 (6.2)
Deaths	1* (0.2)	0	0	1# (0.5)	0

- *Reported as cardiac arrest and adjudicated as death of undetermined cause. #Motor vehicle accident.
ADA, adalimumab; AE, adverse event; b, biologic; DMARD, disease-modifying anti-rheumatic drug; EOW, every other week; IR, inadequate response; PBO, placebo; PsA, psoriatic arthritis; QD, once daily; UPA, upadacitinib.

1. McInnes I et al. Ann Rheum Dis 2020;79(Suppl 1):12;
2. Genovese MC et al. Ann Rheum Dis 2020;79(Suppl 1):139.

SELECT-PsA 1 and 2
Adverse events of interest through Week 24

	SELECT-PsA 1 (DMARD-IR)[1]			SELECT-PsA 2 (bDMARD-IR)[2]	
n (%)	PBO N=423	UPA 15 mg QD N=429	ADA 40 mg EOW N=429	PBO N=212	UPA 15 mg QD N=211
Infection	140 (33.1)	169 (39.4)	146 (34.0)	73 (34.4)	71 (33.6)
Serious infection	4 (0.9)	5 (1.2)	3 (0.7)	1 (0.5)	1 (0.5)
Opportunistic infection	0	1 (0.2)	0	0	0
Herpes Zoster	3 (0.7)	4 (0.9)	0	2 (0.9)	3 (1.4)
Active tuberculosis	0	0	0	0	0
Malignancy	1 (0.2)	1 (0.2)	3 (0.7)	0	3 (1.4)
NMSC	1 (0.2)	0	0	0	1 (0.5)
Lymphoma	0	0	0	0	1* (0.5)
Malignancy other than NMSC	0	1 (0.2)	3 (0.7)	0	2 (0.9)
Hepatic disorder	16 (3.8)	39 (9.1)	67 (15.6)	3 (1.4)	4 (1.9)
GI perforation (adjudicated)	0	0	0	0	0

*Adverse events of atypical lymphocytes; Opportunistic infection = any opportunistic infection excluding tuberculosis and herpes zoster.
ADA, adalimumab; b, biologic; DMARD, disease-modifying anti-rheumatic drug; EOW, every other week; GI, gastrointestinal; IR, inadequate response; NMSC, non-melanoma skin cancer; PBO, placebo; PsA, psoriatic arthritis; QD, once daily; UPA, upadacitinib.

1. McInnes I et al. Ann Rheum Dis 2020;79(Suppl 1):12;
2. Genovese MC et al. Ann Rheum Dis 2020;79(Suppl 1):139.

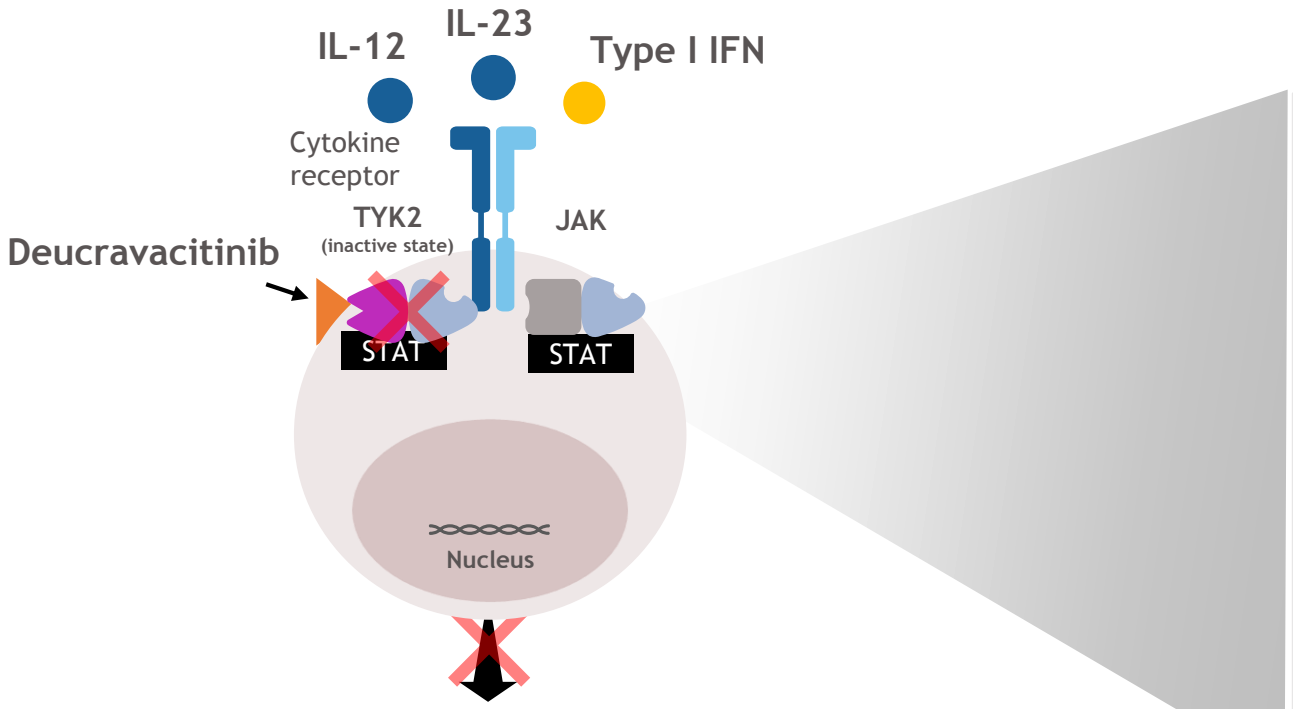
SELECT-PsA 1 and 2
Adverse events of interest through Week 24

	SELECT-PsA 1 (DMARD-IR)[1]			SELECT-PsA 2 (bDMARD-IR)[2]	
n (%)	PBO N=423	UPA 15 mg QD N=429	ADA 40 mg EOW N=429	PBO N=212	UPA 15 mg QD N=211
Anemia	4 (0.9)	3 (0.7)	1 (0.2)	2 (0.9)	4 (1.9)
Neutropenia	1(0.2)	4 (0.9)	10 (2.3)	1 (0.5)	2 (0.9)
Lymphopenia	5 (1.2)	6 (1.4)	1 (0.2)	0	2 (0.9)
CPK elevation	6 (1.4)	38 (8.9)	24 (5.6)	4 (1.9)	4 (1.9)
Renal dysfunction	1 (0.2)	0	0	1 (0.5)	0
MACE (adjudicated)	1 (0.2)	0	2 (0.5)	0	1 (0.5)
VTE (adjudicated)	1 (0.2)	0	2 (0.5)	0	1 (0.5)

ADA, adalimumab; b, biologic; CPK, creatine phosphokinase; DMARD, disease-modifying anti-rheumatic drug; EOW, every other week; IR, inadequate response; MACE, major adverse cardiovascular events; PBO, placebo; PsA, psoriatic arthritis; QD, once daily; SD, standard deviation; UPA, upadacitinib; VTE, venous thromboembolic events.

1. McInnes I et al. Ann Rheum Dis 2020;79(Suppl 1):12;
2. Genovese MC et al. Ann Rheum Dis 2020;79(Suppl 1):139.

Deucravacitinib: an oral, selective, small–molecule, allosteric inhibitor of TYK2

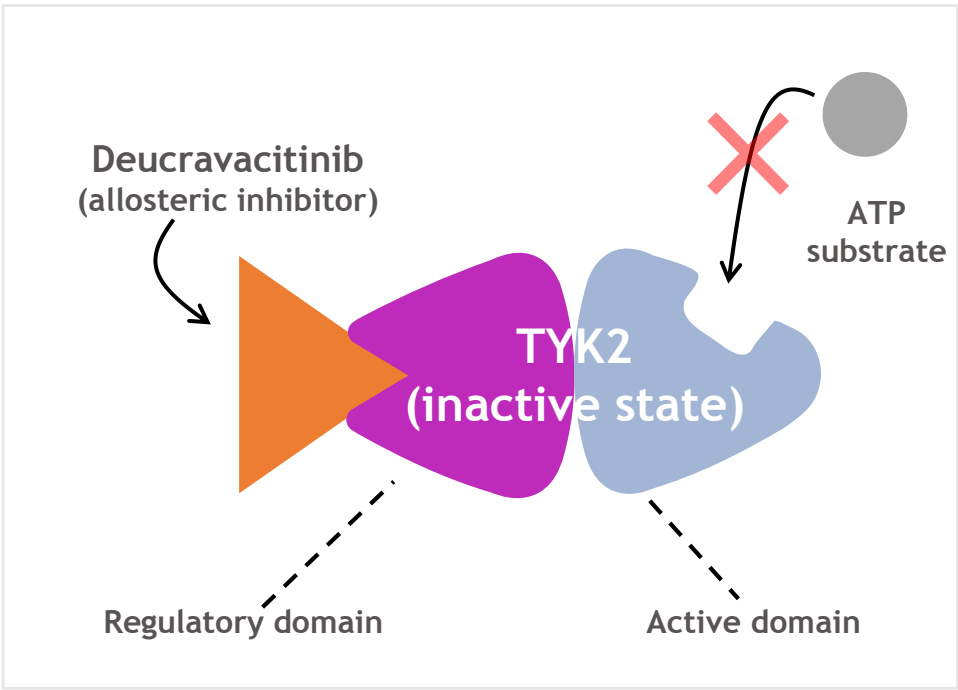


Immune-specific responses[4-7]

Pro-inflammatory cytokine signaling and downstream effects (e.g. IL-23, IL-17)

Immune cell survival, function, and activation (e.g. Th1, Th17)

Allosteric inhibition of TYK2[8,9]



Allosteric inhibition by deucravacitinib locks TYK2 in the inactive state, preventing downstream cytokine signaling[8,9]

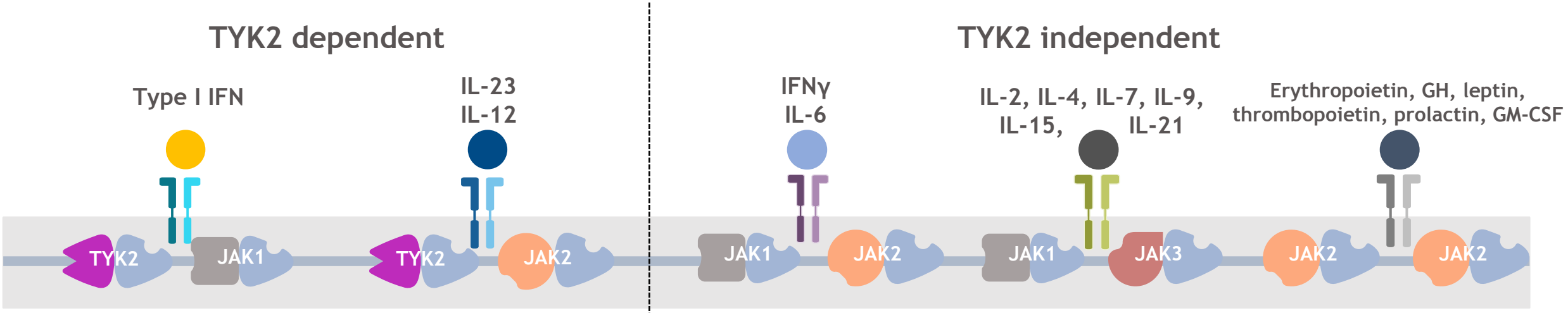
Adapted from *J Med Chem*,[1] *Sci Transl Med*,[3] and *Ann Rheum Dis*[5]

The relationship of these biological response markers to the mechanisms by which deucravacitinib exerts its clinical effects is unknown. There are additional cytokines in the TYK2 pathway beyond IL-12, Il-23, and IFNα/β.

ATP, adenosine triphosphate; IFN, interferon; IL, interleukin; JAK, Janus kinase; STAT, signal transducer and activator of transcription; Th, helper T; TYK2, tyrosine kinase 2.

1. Wrobleski ST et al. *J Med Chem*. 2019;62:8973–8995. 2. Papp K et al. *N Engl J Med*. 2018;379:1313–1321. 3. Burke JR et al. *Sci Transl Med*. 2019;11:eaaw1736. 4. Hawkes JE et al. *J Allergy Clin Immunol*. 2017;140:645–653. 5. Baker KF, Isaacs JD. *Ann Rheum Dis*. 2018;77:175–187. 6. Ghoreschi K et al. *Immunol Rev*. 2009;228:273–287. 7. Seif F et al. *Cell Commun Signal*. 2017;15:23. 8. Borzilleri RM et al. *Burger's Medicinal Chemistry, Drug Discovery and Development*. 8th ed. John Wiley & Sons; 2021. 9. Tokarski JS et al. *J Biol Chem*. 2015;290:11061-11074.

TYK2-dependent and TYK2–independent pathways



- Dendritic cell maturation
- B-cell differentiation
- Antibody production
- T-cell survival
- MHC expression

- Th1 differentiation
- Th17 differentiation
- ILC activation
- Dendritic cell activation
- IL-17, TNFα and IFNγ secretion

- Th1 differentiation
- Osteoclast formation
- Neuronal survival
- Lipid metabolism
- Granulopoiesis

- Lymphoid cell maturation and function
- T-cell survival
- Th2 differentiation
- Treg maintenance

- Hematopoiesis
- Growth factor response
- Metabolic activity regulation
- Myelopoiesis

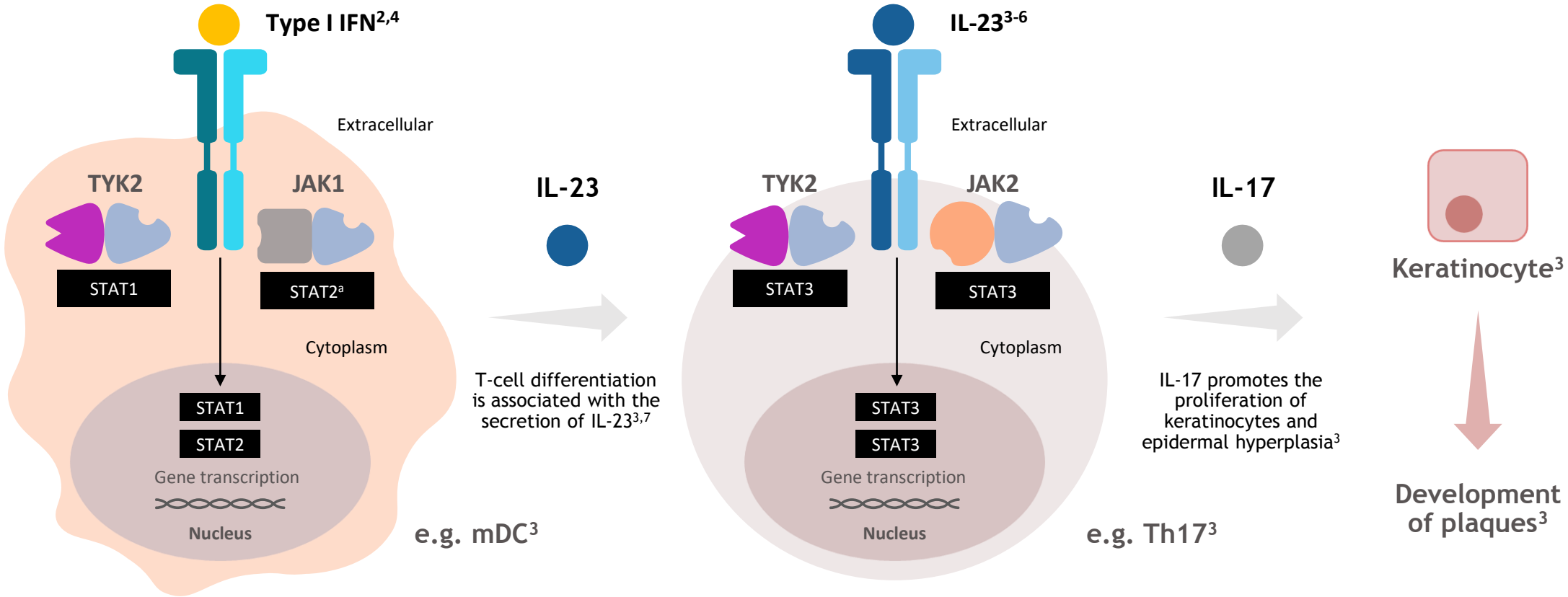
Immune responses
Non-immune homeostatic functions

Adapted with permission from *Immunotherapy*[4]

GH, growth hormone; GM-CSF, granulocyte-macrophage colony-stimulating factor; IFN, interferon; IL, interleukin; ILC, innate lymphoid cell; JAK, Janus kinase; MHC, major histocompatibility complex; Th, helper T cell; TNFα, tumor necrosis factor alpha; Treg, regulatory T cell; TYK2, tyrosine kinase 2.

1. Wrobleski ST et al. *J Med Chem.* 2019;62:8973–8995. 2. Burke JR et al. *Sci Transl Med.* 2019;11:502. 3. Baker KF, Isaacs JD. *Ann Rheum Dis*. 2018;77:175–187. 4. Gonciarz M et al. *Immunotherapy*. 2021;13:1135-1150. 5. Morris R et al. *Protein Sci*. 2018;27:1984–2009. 6. Marroqui L et al. *Diabetes*. 2015;64:3808–3817. Goldstein JD et al. *PLoS ONE.* 2016;11:e0153682.

Type I IFN, IL-23, and IL-17 play critical roles in the pro-inflammatory signaling pathways that lead to the development of psoriasis



IL-23/Th17 axis in psoriasis and psoriatic arthritis[1]

Adapted with permission from *Immunotherapy*[3]
[a]Type I IFN signaling can also induce formation of STAT1/1 homodimers.[2]
IFN, interferon; IL, interleukin; JAK, Janus kinase; mDC, myeloid dendritic cell; STAT, signal transducer and activator of transcription; Th, helper T; TYK2, tyrosine kinase 2.
1. Blauvelt A, Chiricozzi A. *Clin Rev Allergy Immunol*. 2018;55:379–390. 2. Chen K et al. *J Autoimmun*. 2017;83:1–11. 3. Gonciarz M et al. *Immunotherapy*. 2021;13:1135-1150. 4. Hawkes JE et al. *J Allergy Clin Immunol*. 2017;140:645–653. 5. Di Cesare A et al. *J Invest Dermatol*. 2009;129:1339–1350. 6. Coskun M et al. *Pharmacol Res*. 2013;76:1–8. 7. Delgoffe GM, Vignali DAA. *JAKSTAT*. 2013;2:e23060.

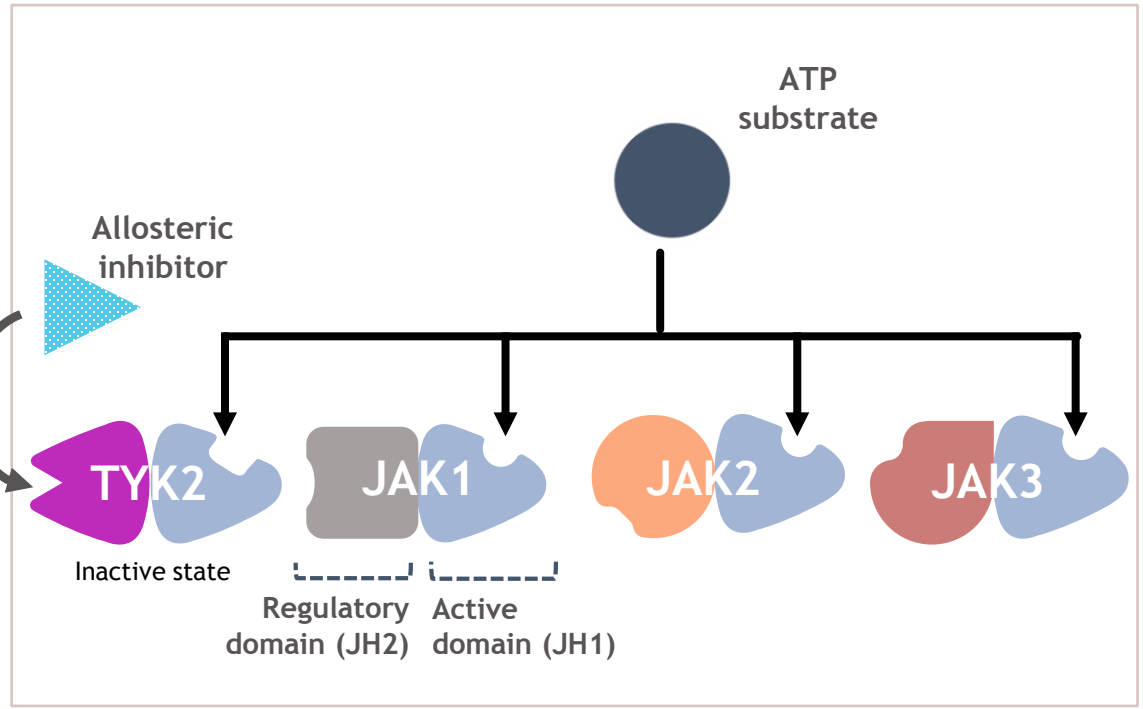
Systems affected by different cytokines mediated through TYK2 and JAK1/2/3 pairs

Systems affected by select pairings	JAK1	JAK2	JAK3	TYK2
Immune system[1–3]	✓	✓	✓	✓
Blood cell development[2,3]		✓		
Metabolic activity[3–5]	✓	✓	✓	
Lipid metabolism[6]	✓	✓		

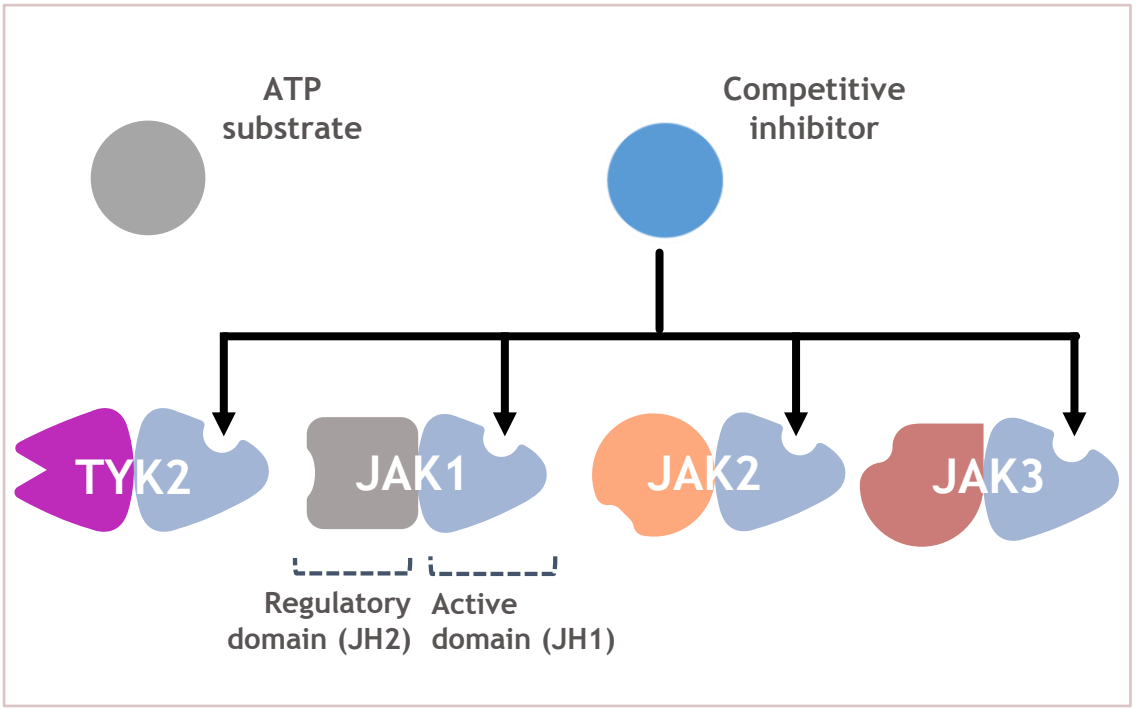
Adapted from *Immunol Rev*,[1] *J Med Chem*,[2] *Protein Sci*,[3] *Cytokine*,[4] *Front Physiol*,[5] and *JAKSTAT*[6]
Please note that this list of systems affected by the different TYK2 and JAK1/2/3 pairings is not exhaustive.
JAK, Janus kinase; TYK2, tyrosine kinase 2.
1. Ghoreschi K et al. *Immunol Rev*. 2009;228:273–287. 2. Clark JD et al. *J Med Chem*. 2014;57:5023–5038. 3. Morris R et al. *Protein Sci*. 2018;27:1984–2009. 4. Hammarén HM et al. *Cytokine*. 2019;118:48–63. 5. Krolopp JE et al. *Front Physiol*. 2016;7:626. 6. Xu D et al. *JAKSTAT*. 2013;2:e27203.

Allosteric inhibition provides greater selectivity for an enzyme

Allosteric inhibition[1,4-8]



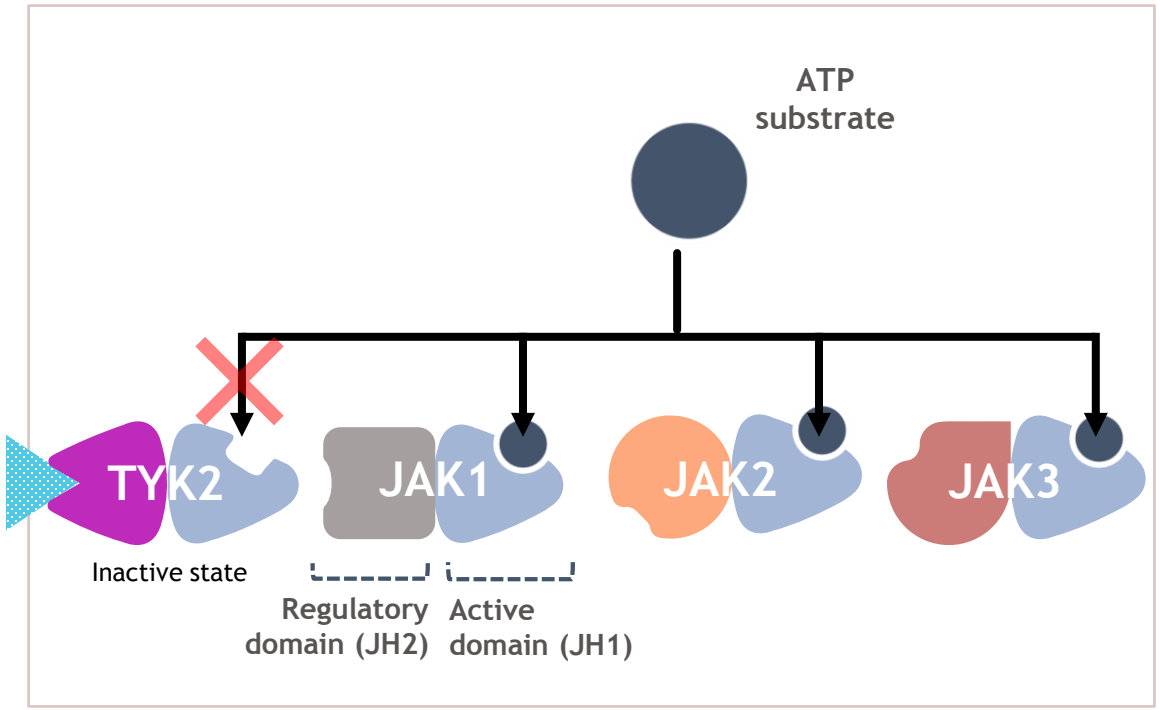
Competitive inhibition[1,6-8]



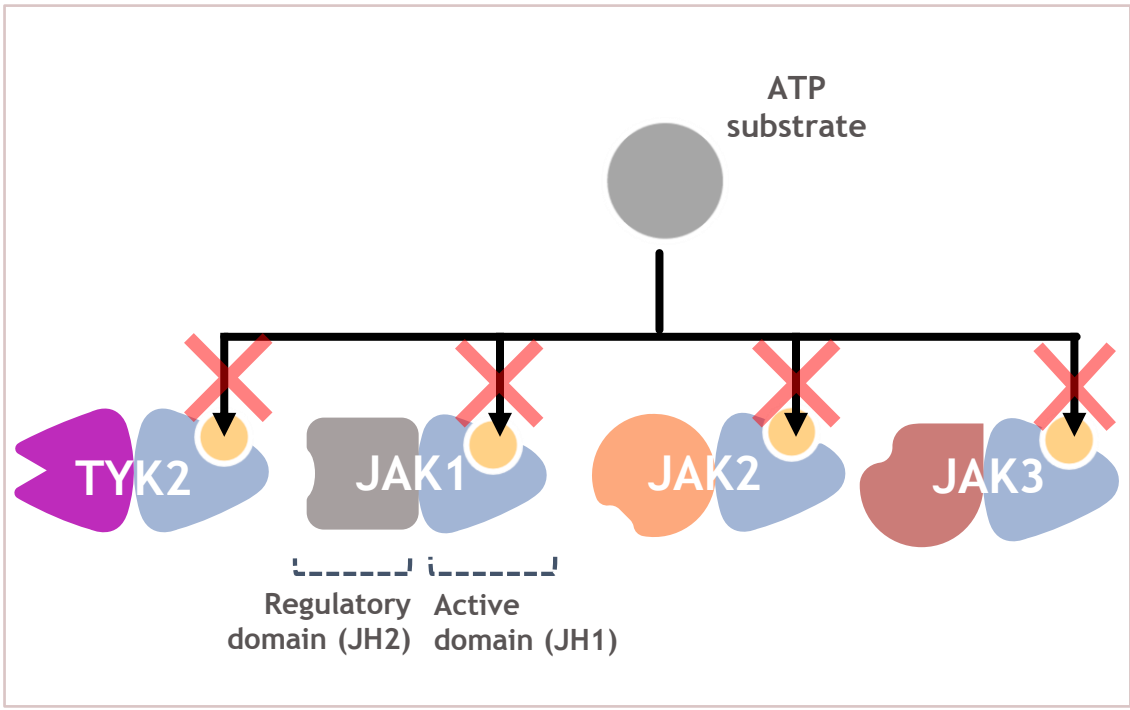
Adapted from *Cell*,[1] *Biochemistry*,[6] *Assay Guidance Manual*,[7] and *Angew Chem Int Ed Engl*[8]
ATP, adenosine triphosphate; JAK, Janus kinase; JH, Janus homology; TYK2, tyrosine kinase 2.
1. Nussinov R, Tsai C-J. *Cell*. 2013;153:293-305. 2. Imai K, Takaoka A. *Nat Rev Cancer*. 2006;6:714-727. 3. Krueger JG et al. *J Am Acad Dermatol*. 2022;86:148-157. 4. Borzilleri RM et al. *Burger's Medicinal Chemistry, Drug Discovery and Development*. 8th ed. John Wiley & Sons; 2021. 5. Tokarski JS et al. *J Biol Chem*. 2015;290:11061–11074. 6. Berg JM et al. *Biochemistry*. 5th ed. New York: WH Freeman; 2002. 7. Strelow J et al. In: Markossian S et al. eds. Eli Lilly & Company and the National Center for Advancing Translational Sciences. *Assay Guidance Manual*. 2021;1329-1379. 8. Lu X et al. *Angew Chem Int Ed Engl*. 2020;59:13764-13776.

Allosteric inhibition provides greater selectivity for an enzyme

Allosteric inhibition[1,4-8]



Competitive inhibition[1,6-8]



- Allosteric inhibitors tend to target less conserved sites vs competitive inhibitors[1]
- Allosteric inhibition can prevent ATP from binding to the active domain by locking the active site in an inactive state[3,4]
- This results in a high degree of specificity with allosteric inhibitors[1]

Adapted from *Cell*,[1] *Biochemistry*,[6] *Assay Guidance Manual*,[7] and *Angew Chem Int Ed Engl*[8]
ATP, adenosine triphosphate; JAK, Janus kinase; JH, Janus homology; TYK2, tyrosine kinase 2.
1. Nussinov R, Tsai C-J. *Cell*. 2013;153:293–305. 2. Imai K, Takaoka A. *Nat Rev Cancer*. 2006;6:714-727. 3. Krueger JG et al. *J Am Acad Dermatol*. 2022;86:148-157. 4. Borzilleri RM et al. *Burger's Medicinal Chemistry, Drug Discovery and Development*. 8th ed. John Wiley & Sons; 2021. 5. Tokarski JS et al. *J Biol Chem*. 2015;290:11061–11074. 6. Berg JM et al. *Biochemistry*. 5th ed. New York: WH Freeman; 2002. 7. Strelow J et al. In: Markossian S et al. eds. Eli Lilly & Company and the National Center for Advancing Translational Sciences. *Assay Guidance Manual*. 2021;1329-1379. 8. Lu X et al. *Angew Chem Int Ed Engl*. 2020;59:13764-13776.

Deucravacitinib

Approved by FDA in September 2022 and by EMA in March 2023

4. INFORMAZIONI CLINICHE

4.1 Indicazioni terapeutiche

SOTYKTU è indicato per il trattamento della psoriasi a placche da moderata a severa in adulti candidati alla terapia sistemica.

4.2 Posologia e modo di somministrazione

Il trattamento deve essere iniziato dietro indicazione e con la supervisione di un medico esperto nella diagnosi e nel trattamento della psoriasi.

Posologia

La dose raccomandata è di 6 mg per via orale una volta al giorno.

Se un paziente non mostra evidenze di beneficio terapeutico dopo 24 settimane, deve essere presa in considerazione l'interruzione del trattamento. La risposta del paziente al trattamento deve essere valutata regolarmente.

Popolazioni speciali

Anziani
Non sono necessari adeguamenti della dose in pazienti anziani di età pari o superiore a 65 anni (vedere paragrafo 5.2). L'esperienza clinica nei pazienti di età ≥ *75* anni è molto limitata e deucravacitinib deve essere usato con cautela in questo gruppo di pazienti.

Compromissione renale
Non sono necessari adeguamenti della dose in pazienti con compromissione renale, inclusi pazienti con nefropatia allo stadio terminale (ESRD) in dialisi (vedere paragrafo 5.2).

Compromissione epatica
Non sono necessari adeguamenti della dose in pazienti con compromissione epatica lieve o moderata. L'uso di deucravacitinib non è raccomandato in pazienti con compromissione epatica severa (vedere paragrafo 5.2).

Popolazione pediatrica
La sicurezza e l'efficacia di deucravacitinib nei bambini e negli adolescenti di età inferiore a 18 anni non sono state ancora stabilite. Non ci sono dati disponibili.

Modo di somministrazione

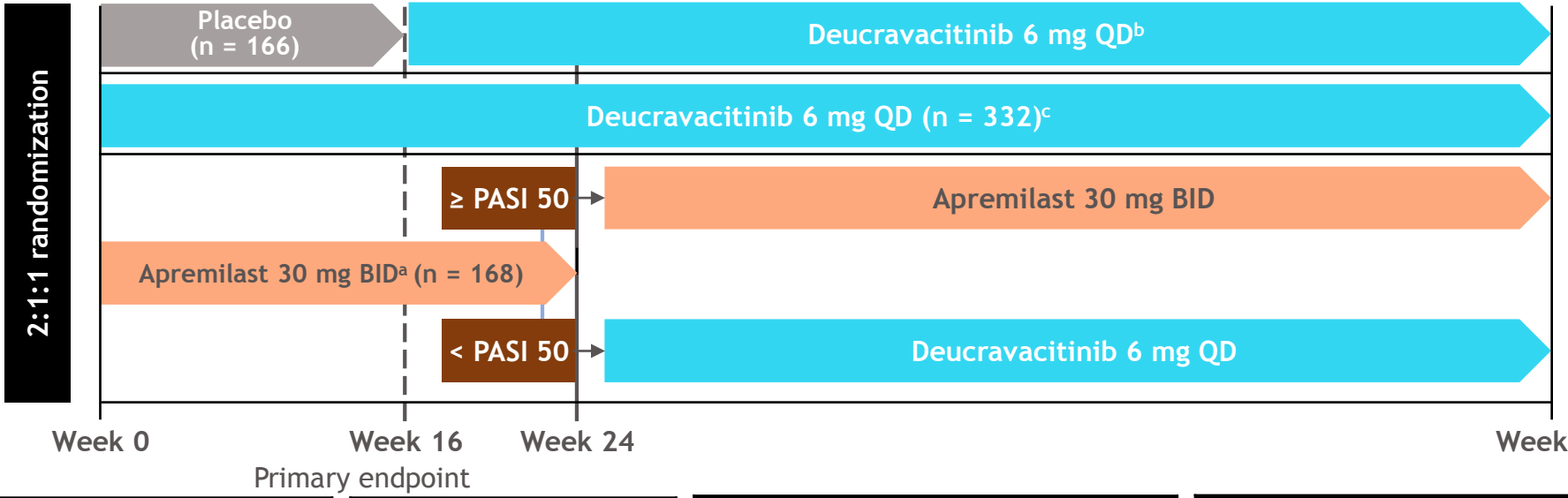
Per uso orale.

Le compresse possono essere assunte con o senza cibo. Le compresse devono essere deglutite intere e non devono essere frantumate, tagliate o masticate.

RCP - Documento reso disponibile da AIFA il 01/09/2023

POETYK PSO-1: study design

Potential indication: Moderate to severe psoriasis
Design: Phase 3, multicenter, randomized, double-blind, placebo- and active comparator–controlled study[1,2]



All patients were eligible for a long-term extension study after 52 weeks of treatment[1]

Patients (N = 666)[1]

Key inclusion criteria
- Adults with moderate to severe plaque psoriasis
- PASI ≥ 12, sPGA ≥ 3, BSA ≥ 10%

Stratification factors[1]
- Geographic region
- Body weight
- Prior biologic use

Primary endpoints[1]

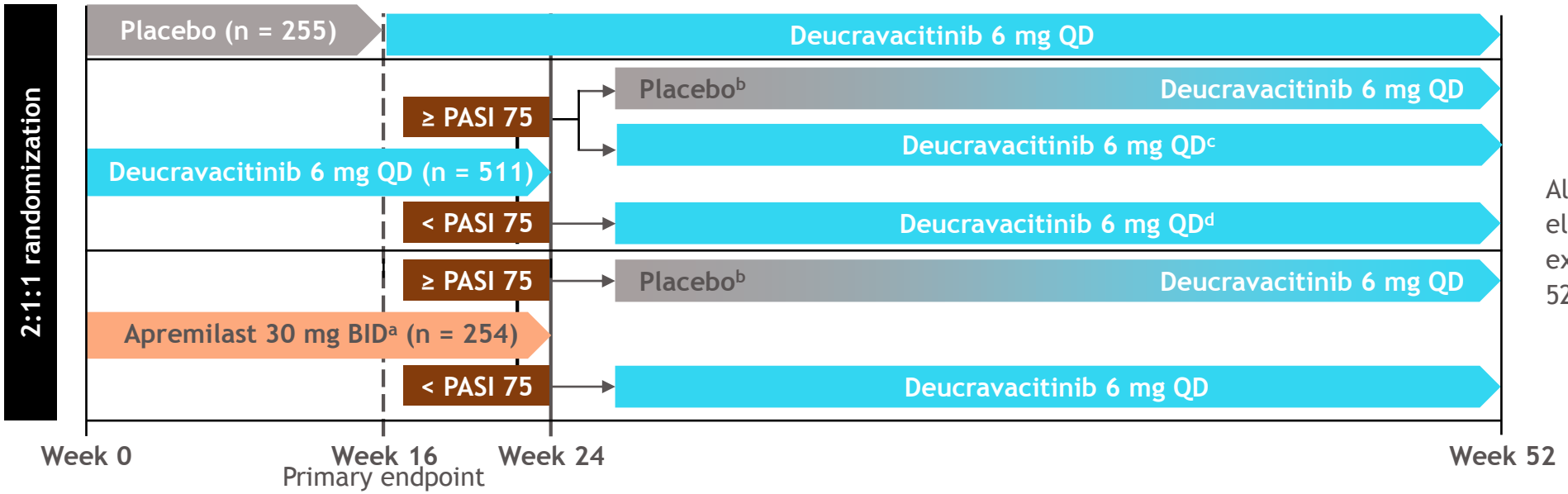
Co-primary endpoints at Week 16 comparing deucravacitinib vs placebo[1]
- PASI 75
- sPGA 0/1

Completion rates through Week 16[1]
- Deucravacitinib: 92.5%
- Placebo: 87.9%
- Apremilast: 86.3%

This slide contains hyperlinks.
[a]Apremilast was titrated from 10 mg QD to 30 mg BID over the first 5 days of dosing.[1] [b]A total of 78.2% of patients who switched to deucravacitinib from placebo at Week 16 continued to Week 52.[3] [c]A total of 80.7% of patients completed 52 weeks of deucravacitinib treatment.[3]
BID, twice daily; BSA, body surface area; PASI, Psoriasis Area and Severity Index; PASI 50/75, 50%/75% improvement in PASI score; QD, once daily; sPGA, static Physician's Global Assessment.
1. Armstrong AW et al. Oral presentation at AAD VMX; April 23–25, 2021; Virtual. 2. ClinicalTrials.gov. Accessed September 2021. https://clinicaltrials.gov/ct2/show/NCT03624127 3. Warren RB et al. Oral presentation at EADV Annual Meeting; September 29–October 2, 2021; Virtual. Abstract 2857.

POETYK PSO-2: study design

Potential indication: Moderate to severe psoriasis
Design: Phase 3, multicenter, randomized, double-blind, placebo- and active comparator–controlled study[1,2]



All patients were eligible for a long-term extension study after 52 weeks of treatment[1]

Patients (N = 1020)[1]

Key inclusion criteria
- Adults with moderate to severe plaque psoriasis
- PASI ≥ 12, sPGA ≥ 3, BSA ≥ 10%

Stratification factors[1]
- Geographic region
- Body weight
- Prior biologic use

Primary endpoints[1]

Co-primary endpoints at Week 16 comparing deucravacitinib vs placebo[1]
- PASI 75
- sPGA 0/1

Completion rates through Week 16[1]
- Deucravacitinib: 89.4%
- Placebo: 83.5%
- Apremilast: 85.4%

This slide contains hyperlinks.

[a]Apremilast was titrated from 10 mg QD to 30 mg BID over the first 5 days of dosing.[1] [b]Any patient who switched from deucravacitinib or apremilast to placebo at Week 24 and subsequently experienced a relapse (≥50% loss of Week 24 percentage improvement from baseline in PASI) was to be switched to deucravacitinib as outlined in the study protocol. However, due to a programming error, this did not occur and patients remained on placebo until they entered the POETYK LTE at Week 52.[4] [c]93.2% of patients who achieved a PASI 75 response and rerandomized to continue receiving deucravacitinib at Week 24 completed 52 weeks of treatment.[3] [d]A total of 142 patients did not achieve PASI 75 by Week 24 and continued to receive deucravacitinib until Week 52.[3]

BID, twice daily; BSA, body surface area; PASI, Psoriasis Area and Severity Index; PASI 75, 75% improvement in PASI score; QD, once daily; sPGA, static Physician's Global Assessment.

1. Armstrong AW et al. Oral presentation at AAD VMX; April 23–25, 2021; Virtual. 2. ClinicalTrials.gov. Accessed September 2021. https://clinicaltrials.gov/ct2/show/NCT03611751 3. Warren RB et al. Oral presentation at EADV Annual Meeting; September 29–October 2, 2021; Virtual. Abstract 2857. 4. Warren RB et al. Poster presentation at EADV Congress; September 7-10, 2022; Milan, IT. Poster 1456.

POETYK PSO-1: baseline demographics and disease characteristics

Parameter	Placebo (n = 166)	Deucravacitinib (n = 332)	Apremilast (n = 168)	Total (N = 666)
Age, years, mean [SD]	47.9 [14.0]	45.9 [13.7]	44.7 (12.1)	46.1 [13.4]
Weight, kg, mean [SD]	89.1 [22.3]	87.9 [21.8]	87.5 [21.1]	88.1 [21.7]
BMI, kg/m², mean [SD]	30.24 [7.4]	29.77 [7.0]	29.64 (6.7)	29.85 [7.0]
Sex, n (%)				
Male	113 (68.1)	230 (69.3)	110 (65.5)	453 (68.0)
Female	53 (31.9)	102 (30.7)	58 (34.5)	213 (32.0)
Race, n (%)				
White	128 (77.1)	267 (80.4)	139 (82.7)	534 (80.2)
Black or African American	3 (1.8)	2 (0.6)	1 (0.6)	6 (0.9)
Asian	34 (20.5)	59 (17.8)	28 (16.7)	121 (18.2)
Other	1 (0.6)	4 (1.2)	0 (0.0)	5 (0.8)
Age at disease onset, years, mean [SD]	31.5 [14.7]	29.6 [15.1]	27.8 [13.1]	29.6 [14.6]
Disease duration, years, mean [SD]	17.3 [12.8]	17.1 [12.4]	17.7 [11.8]	17.3 [12.3]
sPGA score (0–4), n (%)				
3 (moderate)	128 (77.1)	257 (77.4)	139 (82.7)	524 (78.7)
4 (severe)	37 (22.3)	75 (22.6)	29 (17.3)	141 (21.2)
PASI (0–72), mean [SD]	20.7 [8.0]	21.8 [8.6]	21.4 [9.0]	21.4 [8.6]

Parameter	Placebo (n = 166)	Deucravacitinib (n = 332)	Apremilast (n = 168)	Total (N = 666)
BSA involvement, %, mean [SD]	25.3 [16.9]	26.6 [15.9]	26.6 [16.1]	26.3 [16.2]
DLQI (0–30), mean [SD]	11.4 [6.6]	12.0 [6.7]	12.4 [6.8]	12.0 [6.7]
PSSD symptom score (0–100), mean [SD]	51.4 [26.8]	51.7 [25.2]	56.2 [25.2]	52.8 [25.6]
ss-PGA ≥ 3, n (%)	121 (72.9)	209 (63.0)	110 (65.5)	440 (66.1)
Psoriasis-related history, n (%)				
Scalp	155 (93.4)	298 (89.8)	156 (92.9)	609 (91.4)
Nails	76 (45.8)	138 (41.6)	64 (38.1)	278 (41.7)
Psoriatic arthritis	26 (15.7)	64 (19.3)	31 (18.5)	121 (18.2)
Prior systemic treatment use, n (%)				
Yes	109 (65.7)	200 (60.2)	109 (64.9)	418 (62.8)
Biologic[a]	63 (38.0)	130 (39.2)	66 (39.2)	259 (38.9)
Nonbiologic	46 (27.7)	70 (21.1)	43 (25.6)	159 (23.9)
No prior systemic therapy	57 (34.3)	132 (39.8)	59 (35.1)	248 (37.2)

This slide contains hyperlinks.

[a]**Including tumor necrosis factor inhibitors or antibodies to IL-23p19, IL-12/23p40, or IL-17.**

BMI, body mass index; BSA, body surface area; DLQI, Dermatology Life Quality Index; IL, interleukin; PASI, Psoriasis Area and Severity Index; PRO, patient-reported outcome; PSSD, Psoriasis Symptoms and Signs Diary; sPGA, static Physician's Global Assessment; ss-PGA, scalp-specific Physician's Global Assessment.

Armstrong AW et al. *J Am Acad Dermatol*. 2022. doi:10.1016/j.jaad.2022.07.002.

POETYK PSO-2: baseline demographics and disease characteristics

Parameter	Placebo (n = 255)	Deucravacitinib (n = 511)	Apremilast (n = 254)	Total (N = 1020)
Age, years, mean [SD]	47.3 [13.6]	46.9 [13.4]	46.4 [13.3]	46.9 [13.4]
Weight, kg, mean [SD]	91.5 [20.2]	92.3 [21.9]	93.5 [22.2]	92.4 [21.6]
BMI, kg/m², mean [SD]	30.4 [6.3]	31.0 [6.8]	31.6 [7.2]	31.0 [6.8]
Sex, n (%)				
Male	181 (71.0)	336 (65.8)	157 (61.8)	674 (66.1)
Female	74 (29.0)	175 (34.2)	97 (38.2)	346 (33.9)
Race, n (%)				
White	232 (91.0)	474 (92.8)	229 (90.2)	935 (91.7)
Black or African American	9 (3.5)	8 (1.6)	9 (3.5)	26 (2.5)
Asian	8 (3.1)	24 (4.7)	12 (4.7)	44 (4.3)
Other	6 (2.4)	5 (1.0)	4 (1.6)	15 (1.5)
Age at disease onset, years, mean [SD]	28.4 [15.5]	28.2 [14.7]	28.4 [15.7]	28.3 [15.1]
Disease duration, years, mean [SD]	19.9 [12.9]	19.6 [12.9]	18.9 [12.4]	19.5 [12.7]
sPGA score (0–4), n (%)				
3 (moderate)	217 (85.1)	408 (79.8)	196 (77.2)	821 (80.5)
4 (severe)	38 (14.9)	103 (20.2)	58 (22.8)	199 (19.5)
PASI (0–72), mean [SD]	21.1 [9.0]	20.7 [7.5]	21.6 [8.4]	21.0 [8.1]

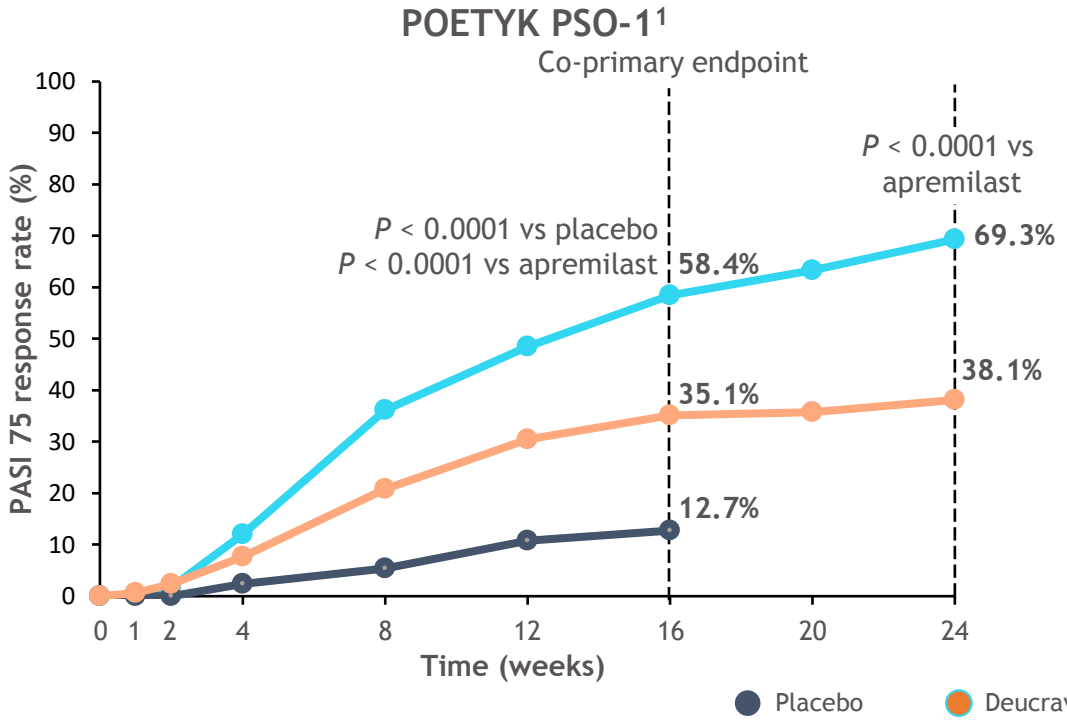
Parameter	Placebo (n = 255)	Deucravacitinib (n = 511)	Apremilast (n = 254)	Total (N = 1020)
BSA involvement, %, mean [SD]	25.3 [15.7]	26.3 [15.8]	28.3 [16.5]	26.5 [16.0]
DLQI (0–30), mean [SD]	11.8 [6.8]	11.8 [6.5]	12.5 [6.7]	12.0 [6.6]
PSSD symptom score (0–100), mean [SD]	50.1 [24.8]	52.3 [26.3]	51.9 [25.4]	51.6 [25.7]
ss-PGA ≥ 3, n (%)	173 (67.8)	305 (59.7)	166 (65.4)	644 (63.1)
Psoriasis-related history, n (%)				
Scalp	226 (88.6)	446 (87.3)	228 (89.8)	900 (88.2)
Nails	119 (46.7)	227 (44.4)	125 (49.2)	471 (46.2)
Psoriatic arthritis	45 (17.6)	100 (19.6)	45 (17.7)	190 (18.6)
Prior systemic treatment use, n (%)				
Yes	139 (54.5)	274 (53.6)	140 (55.1)	553 (54.2)
Biologic	83 (32.5)	165 (32.3)	79 (31.1)	327 (32.1)
Nonbiologic	56 (22.0)	109 (21.3)	61 (24.0)	226 (22.2)
No prior systemic therapy	116 (45.5)	237 (46.4)	114 (44.9)	467 (45.8)

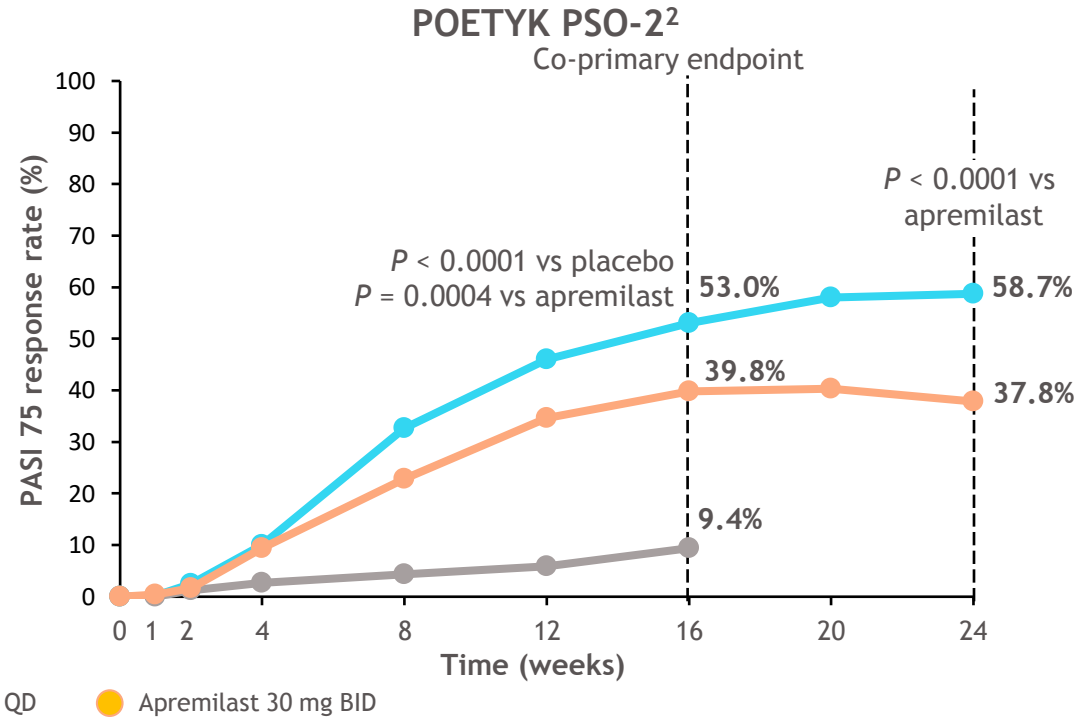
This slide contains hyperlinks.

BMI, body mass index; BSA, body surface area; DLQI, Dermatology Life Quality Index; PASI, Psoriasis Area and Severity Index; PRO, patient-reported outcome; PSSD, Psoriasis Symptoms and Signs Diary; sPGA, static Physician's Global Assessment; ss-PGA, scalp-specific Physician's Global Assessment.

Strober B et al. *J Am Acad Dermatol*. 2022. doi:10.1016/j.jaad.2022.08.061.

Co-primary endpoint: PASI 75 response at Week 16, and through Week 24 (NRI)





- A significantly greater proportion of patients receiving deucravacitinib achieved PASI 75 responses compared with patients receiving placebo ($P < 0.0001$) and apremilast ($P < 0.0001$ in POETYK PSO-1; $P = 0.0004$ in POETYK PSO-2) at Week 16[1,2]
- This statistically significant difference between the deucravacitinib and apremilast arms was also observed at Week 24 ($P < 0.0001$)[1,2]

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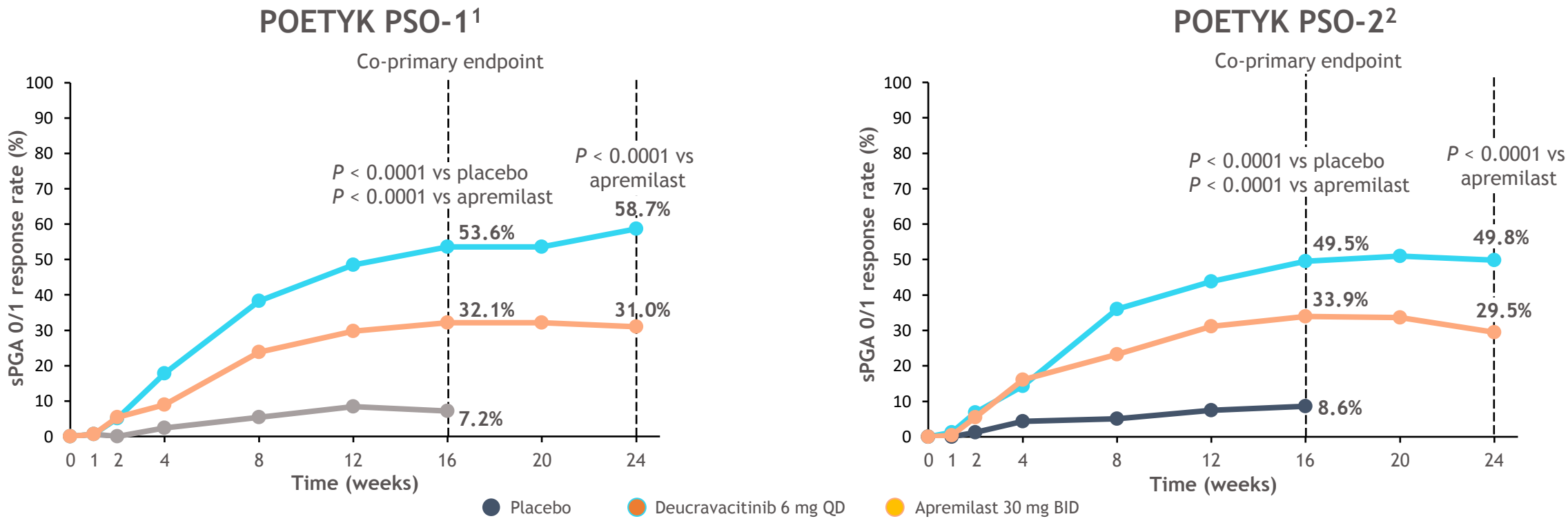
BID, twice daily; NRI, nonresponder imputation; PASI 75, 75% improvement in Psoriasis Area and Severity Index score; QD, once daily.
1. Armstrong AW et al. *J Am Acad Dermatol*. 2022. doi:10.1016/j.jaad.2022.07.002. 2. Warren RB et al. Oral presentation at EADV Annual Meeting; September 29–October 2, 2021; Virtual. Abstract FC03.06.

Co-primary endpoint: sPGA 0/1 response[a] at Week 16, and through Week 24 (NRI)



- A significantly greater proportion of patients receiving deucravacitinib achieved sPGA 0/1 compared with patients receiving placebo ($P < 0.0001$) and apremilast ($P < 0.0001$)[1,2]
- This statistically significant difference between the deucravacitinib and apremilast arms was also observed at Week 24 ($P < 0.0001$) [1,2]

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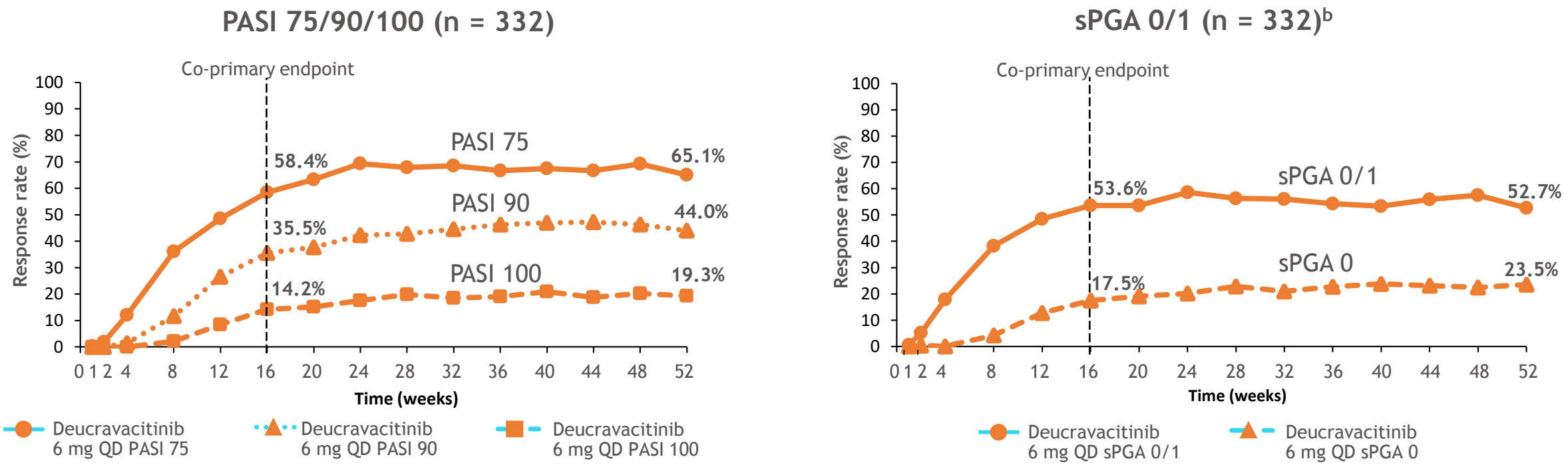
[a]Response defined as sPGA score of 0/1 with ≥ 2-point improvement from baseline.[1,2]
BID, twice daily; NRI, nonresponder imputation; QD, once daily; sPGA 0/1, static Physician's Global Assessment score of 0 or 1.
1. Armstrong AW et al. *J Am Acad Dermatol*. 2022. doi:10.1016/j.jaad.2022.07.002. 2. Warren RB et al. Oral presentation at EADV Annual Meeting; September 29–October 2, 2021; Virtual. Abstract FC03.06.

PASI and sPGA responses with deucravacitinib through Week 52 (NRI)[a]



- PASI 75 and sPGA 0/1 responses (co-primary efficacy endpoints) were maintained from Week 16 to Week 52 in patients who received continuous deucravacitinib treatment from Day 1
- PASI 90, PASI 100, and sPGA 0 responses (secondary efficacy endpoints) were also maintained through 52 weeks in patients treated with deucravacitinib from Day 1

Reproduced with permission from Warren RB.
[a]Missing data were imputed using NRI. [b]sPGA response defined as a score of 0 or 1, with ≥ 2-point improvement from baseline.
NRI, nonresponder imputation; PASI, Psoriasis Area and Severity Index; PASI 75/90/100, 75%/90%/100% improvement in PASI score; sPGA, static Physician's Global Assessment; sPGA 0, sPGA score of 0; sPGA 0/1, sPGA score of 0 or 1.
Warren RB et al. Oral presentation at EADV Annual Meeting; September 29–October 2, 2021; Virtual. Abstract 2857.

Safety summary (integrated): Weeks 0–16

AE category, n (%)	Placebo (n = 419)		Deucravacitinib (n = 842)		Apremilast (n = 422)	
	n (%)	EAIR/ 100 PY	n (%)	EAIR/ 100 PY	n (%)	EAIR/ 100 PY
Any AEs[1,2]	208 (49.6)	263.2	469 (55.7)	305.7	243 (57.6)	341.3
Serious AEs[1,2]	12 (2.9)	9.9	15 (1.8)	6.0	5 (1.2)	4.0
AEs leading to discontinuation[1,2]	16 (3.8)	13.2	20 (2.4)	8.0	22 (5.2)	17.9
Deaths[1,2]	1[a] (0.2)	NR	1[b] (0.1)	NR	1[c] (0.2)	NR
Most common AEs (≥ 5%) in any active treatment group[1,2]						
Nasopharyngitis[1,2]	36 (8.6)	30.6	76 (9.0)	31.7	37 (8.8)	31.1
Upper respiratory tract infection[1,2]	17 (4.1)	14.0	46 (5.5)	18.8	17 (4.0)	13.9
Headache[1,2]	19 (4.5)	16.0	38 (4.5)	15.6	45 (10.7)	39.1
Diarrhea[1,2]	25 (6.0)	21.3	37 (4.4)	15.2	50 (11.8)	43.9
Nausea[1,2]	7 (1.7)	5.8	14 (1.7)	5.6	42 (10.0)	36.4

Reproduced with permission from Alexis A[1] and Armstrong AW.[2]

[a]One 57-year-old female patient receiving placebo experienced sudden cardiac death due to hypertensive cardiovascular disease.[2] [b]One patient discontinued deucravacitinib after 4 days of treatment due to prohibited medication (leflunomide) and died 9 days later due to sepsis and heart failure.[2] [c]One patient discontinued apremilast due to lung cancer after 3 months and died 1 month later due to lung cancer and gastrointestinal bleeding.[2]

AE, adverse event; EAIR, exposure-adjusted incidence rate; NR, not reported; PY, patient-years.

1. Alexis A et al. Poster presented at Winter Clinical Dermatology Conference; January 14–19, 2022; Kauai, HI, and Virtual. 2. Armstrong AW et al. Oral presentation at AAD VMX; April 23–25, 2021; Virtual.

European Academy of Dermatology & Venereology (EADV) 2023;
Oct 11–14, 2023; Berlin, Germany

Deucravacitinib in plaque psoriasis: 3-year safety and efficacy results from the phase 3 POETYK PSO-1 and PSO-2 trials

April W. Armstrong,[1] Mark Lebwohl,[2] Richard B. Warren,[3] Howard Sofen,[1,4] Shinichi Imafuku,[5] Mamitaro Ohtsuki,[6] Lynda Spelman,[7] Thierry Passeron,[8] Kim A. Papp,[9] Renata M. Kisa,[10] Victoria Berger,[10] Eleni Vritzali,[10] Kim Hoyt,[10] Matthew J. Colombo,[10] Subhashis Banerjee,[10] Bruce Strober,[11] Diamant Thaçi,[12] Andrew Blauvelt[13]

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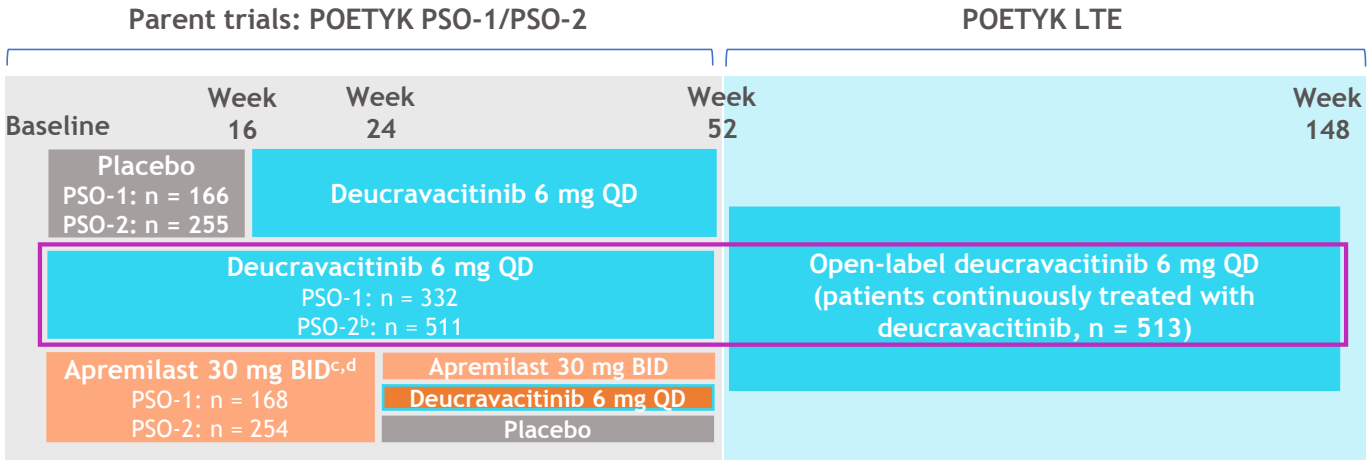
Los Angeles, CA, USA; [5]Fukuoka University Faculty of Medicine, Fukuoka, Japan; [6]Jichi Medical University, Tochigi, Japan; [7]Veracity Clinical Research and Probity Medical Research, Brisbane, QLD, Australia; [8]Université Côte d'Azur, University Hospital of Nice, Nice, France; [9]Alliance Clinical Trials and Probity Medical Research, Waterloo, and the University of Toronto School of Medicine, Toronto, ON, Canada; [10]Bristol Myers Squibb, Princeton, NJ, USA; [11]Yale University School of Medicine, New Haven, and Central Connecticut Dermatology Research, Cromwell, CT, USA; [12]Institute and Comprehensive Center for Inflammation Medicine, University of Lübeck, Lübeck, Germany; [13]Oregon Medical Research Center, Portland, OR, USA

Methods: POETYK PSO-1, PSO-2, and LTE analysis populations

Key eligibility criteria in the parent studies:

- Age ≥18 years
- Moderate to severe plaque psoriasis:
  - PASI ≥12
  - sPGA ≥3
  - BSA involvement ≥10%



- **Analysis populations**
- Safety population: pooled parent trials (POETYK PSO-1 and PSO-2) and the POETYK LTE trial over 3 years in the as-treated population (patients receiving ≥1 dose of deucravacitinib)
  - AEs were ascribed to the treatment group that patients were assigned to when the event first occurred
- Efficacy population: pooled parent trial (POETYK PSO-1 and PSO-2) patients who received continuous deucravacitinib treatment from Day 1 of the parent trials through Week 148

[a]Includes patients with ≥1 dose of deucravacitinib 6 mg QD, n = 1519. [b]In POETYK PSO-2, patients randomized to deucravacitinib on Day 1 who achieved PASI 75 at Week 24 were rerandomized to placebo or deucravacitinib; for patients who were rerandomized to placebo, upon relapse (≥50% loss of Week 24 PASI percent improvement from baseline), they were to cross over to deucravacitinib; however, due to a programming error, these patients continued to receive placebo until Week 52. [c]In POETYK PSO-1, patients who responded to apremilast remained on apremilast. In POETYK PSO-2, patients who responded to apremilast crossed over to placebo and were to cross over to deucravacitinib upon relapse; however, due to a programming error, these patients continued to receive placebo until Week 52. [d]Apremilast was titrated from 10 mg QD to 30 mg BID over the first 5 days of dosing.

AE, adverse event; BID, twice daily; BSA, body surface area; LTE, long-term extension; PASI, Psoriasis Area and Severity Index; PASI 75, ≥75% reduction from baseline in PASI; QD, once daily; sPGA, static Physician Global Assessment.

Results: Baseline patient demographics and disease characteristics for the overall population

- Received ≥1 dose of deucravacitinib across the parent trials (POETYK PSO-1 and PSO-2) and the POETYK LTE trial:
  n = 1519
  - Randomized to deucravacitinib on Day 1: **n = 843**
  - Continuously treated with deucravacitinib from Day 1, completed POETYK PSO-1 and PSO-2 and entered the POETYK LTE trial: **n = 513[a]**

Parameter	Patients receiving continuous deucravacitinib[a] (n = 513)
Age, mean (SD), y	46.9 (13.3)
Weight, mean (SD), kg	89.9 (22.2)
Female, n (%)	159 (31.0)
Race, n (%)	
White	440 (85.8)
Asian	64 (12.5)
Black or African American	5 (1.0)
Other	4 (0.8)
Age at disease onset, mean (SD), y	29.0 (14.7)
Disease duration, mean (SD), y	18.8 (12.6)
PASI score, mean (SD)	21.1 (7.9)
sPGA score, n (%)	
3 (moderate)	401 (78.2)
4 (severe)	112 (21.8)
BSA involvement, mean (SD), %	26.9 (15.8)

[a]Randomized to deucravacitinib in the parent trials and entering the POETYK LTE trial. [b]POETYK PSO-2 was a randomized withdrawal study; patients randomized to deucravacitinib on Day 1 who achieved PASI 75 at Week 24 were rerandomized to placebo or deucravacitinib; for patients who were rerandomized to placebo, upon relapse (≥50% loss of Week 24 PASI percent improvement from baseline), they were to cross over to deucravacitinib; however, due to a programming error, these patients continued to receive placebo until Week 52.

BSA, body surface area; LTE, long-term extension; PASI, Psoriasis Area and Severity Index; PASI 75, ≥75% reduction from baseline in Psoriasis Area and Severity Index; sPGA, static Physician Global Assessment.

Results: Cumulative safety summary through 2 years and 3 years (as-treated population)

- Aside from a slightly higher COVID-19 rate, AE rates through 3 years remained consistent with rates observed through 2 years

AE category	Cumulative through 2 years[a] (POETYK PSO-1 + PSO-2 + LTE)		Cumulative through 3 years[b] (POETYK PSO-1 + PSO-2 + LTE)	
	Deucravacitinib (n = 1519) Total PY = 2482.0		Deucravacitinib (n = 1519) Total PY = 3294.3	
	n (%)	EAIR/100 PY (95% CI)	n (%)	EAIR/100 PY (95% CI)
AEs	1214 (79.9)	**154.4 (146.0-163.4)**	1269 (83.5)	**144.8 (137.1-153.0)**
SAEs	145 (9.5)	**6.1 (5.2-7.2)**	167 (11.0)	**5.5 (4.7-6.4)**
Discontinued treatment due to AEs	69 (4.5)	**2.8 (2.2-3.5)**	78 (5.1)	**2.4 (2.0-3.0)**
Deaths	10 (0.7)[c]	**0.4 (0.2-0.7)**	10 (0.7)[d]	**0.3 (0.2-0.6)**
Most common AEs (EAIR/100 PY ≥5)				
Nasopharyngitis	271 (17.8)	**12.9 (11.5-14.5)**	302 (19.9)	**11.4 (10.2-12.7)**
COVID-19[e]	124 (8.2)	**5.1 (4.3-6.1)**	242 (15.9)	**8.0 (7.1-9.1)**
Upper respiratory tract infection	150 (9.9)	**6.5 (5.6-7.7)**	182 (12.0)	**6.2 (5.4-7.2)**

Not all patients were receiving deucravacitinib 6 mg QD continuously throughout this period.

[a]This represents the pooled POETYK PSO-1, PSO-2, and LTE population through the cutoff date of October 1, 2021. [b]This represents the pooled POETYK PSO-1, PSO-2, and LTE population through the cutoff date of June 15, 2022. [c]In POETYK PSO-1 and PSO-2 through 1 year, 1 patient discontinued deucravacitinib after 4 days of treatment due to prohibited medication (leflunomide) and died 9 days later due to heart failure and sepsis. Another death occurred between Weeks 16 and 52 and was due to hepatocellular carcinoma in a patient with a history of hepatitis C virus infection and liver cirrhosis. After Week 52, 6 deaths were due to COVID-19 (all in patients with risk factors for severe disease), and 1 was due to a ruptured aortic aneurysm in a patient with cardiovascular risk factors. One patient died due to an unknown cause >30 days after discontinuing treatment but was originally included in the 2-year data; this patient was not included in the 3-year data. [d]One additional death was due to COVID-19. [e]POETYK PSO-1, PSO-2, and LTE trials were conducted during the COVID-19 pandemic.

AE, adverse event; CI, confidence interval; EAIR, exposure-adjusted incidence rate; LTE, long-term extension; PY, person-years; QD, once daily; SAE, serious adverse event.

Results: Cumulative AEs of interest through 2 years and 3 years (as-treated population)

- Incidence rates for MACE and malignancies were low and were comparable through 2 and 3 years
- No VTE events or lymphoma were observed in Year 3

AE category	Cumulative through 2 years[a] (POETYK PSO-1 + PSO-2 + LTE)		Cumulative through 3 years[b] (POETYK PSO-1 + PSO-2 + LTE)	
	Deucravacitinib (n = 1519) Total PY = 2482.0		Deucravacitinib (n = 1519) Total PY = 3294.3	
	n (%)	EAIR/100 PY (95% CI)	n (%)	EAIR/100 PY (95% CI)
Serious infections	64 (4.2)	**2.6 (2.0-3.3)**	77 (5.1)	**2.5 (2.0-3.1)**
Herpes zoster				
Herpes zoster[c]	17 (1.1)	**0.7 (0.4-1.1)**	19 (1.3)	**0.6 (0.4-0.9)**
Ophthalmic herpes zoster[d]	1 (0.1)	**0 (0.0-0.3)**	1 (0.1)	**0.03 (0.0-0.22)**
COVID-19				
Serious COVID-19	30 (2.0)	**1.2 (0.8-1.7)**	37 (2.4)	**1.2 (0.8-1.6)**
Serious COVID-19 pneumonia	13 (0.9)	**0.5 (0.3-0.9)**	14 (0.9)	**0.4 (0.3-0.7)**
MACE[e]	9 (0.6)	**0.4 (0.2-0.7)**	11 (0.7)	**0.3 (0.2-0.6)**
VTE[f]	3 (0.2)	**0.1 (0.0-0.4)**	3 (0.2)	**0.1 (0.0-0.3)**
Malignancies	22 (1.4)	**0.9 (0.6-1.3)**	28 (1.8)	**0.9 (0.6-1.3)**
NMSC	11 (0.7)	**0.4 (0.2-0.8)**	14 (0.9)	**0.4 (0.3-0.7)**
Basal cell carcinoma	8 (0.5)	**0.3 (0.2-0.6)**	10 (0.7)	**0.3 (0.2-0.6)**
Squamous cell carcinoma[g]	4 (0.3)	**0.2 (0.1-0.4)**	4 (0.3)	**0.1 (0.0-0.3)**
Malignancies excluding NMSC	12 (0.8)	**0.5 (0.3-0.8)**	15 (1.0)[h]	**0.5 (0.3-0.8)**
Lymphoma	3 (0.2)	**0.1 (0.0-0.4)**	3 (0.2)	**0.1 (0.0-0.3)**
Hodgkin's disease	1 (0.1)	**0 (0.0-0.3)**	1 (0.1)	**0 (0.0-0.2)**
Leukemia	1 (0.1)	**0 (0.0-0.3)**	1 (0.1)	**0 (0.0-0.2)**

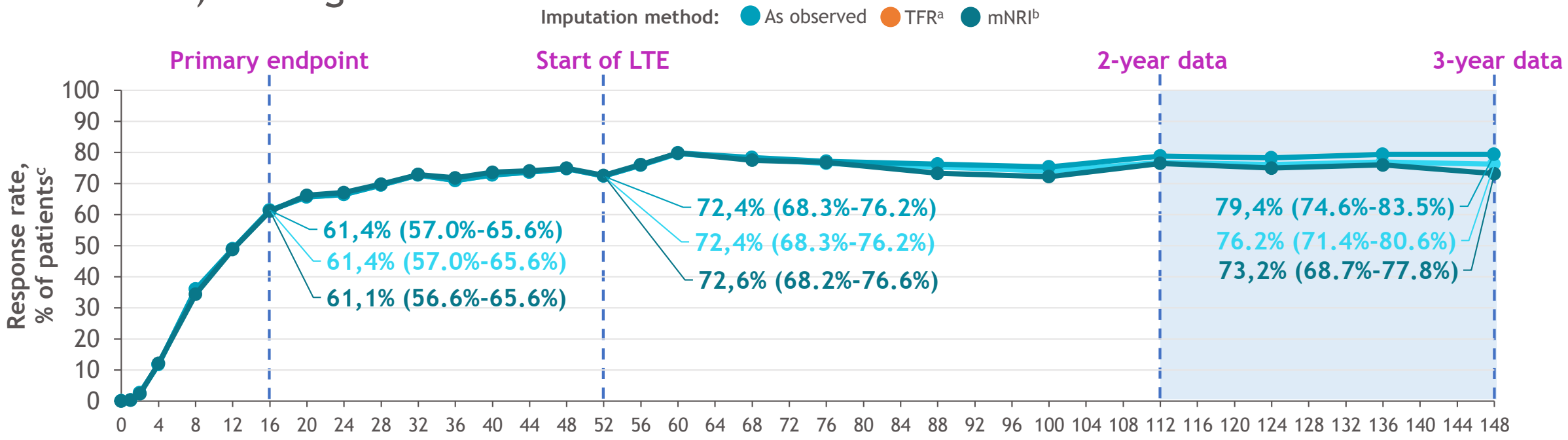
Not all patients were receiving deucravacitinib 6 mg QD continuously throughout this period.

[a]This represents the pooled POETYK PSO-1, PSO-2, and LTE population through the cutoff date of October 1, 2021. [b]This represents the pooled POETYK PSO-1, PSO-2, and LTE population through the cutoff date of June 15, 2022. [c]One patient who was coded as having herpes zoster had corneal/ocular disease related to herpes virus infection diagnosed by an ophthalmologist with a positive qualitative chickenpox virus antigen (epithelial cells). [d]One patient who was coded as having ophthalmic herpes zoster with swelling of eyelids was referred for ophthalmology consultation, which was noted as normal; there was no corneal/ocular disease related to herpes virus infection. [e]MACE were adjudicated and were defined as non-fatal stroke, non-fatal myocardial infarction, or cardiovascular death. [f]VTE was defined as deep vein thrombosis and pulmonary embolism. [g]Includes preferred terms of squamous cell carcinoma, squamous cell carcinoma of skin, and Bowen's disease. [h]Includes events of breast cancer and malignant melanoma (n = 2), and acute promyelocytic leukemia, B-cell lymphoma, colon cancer, colorectal cancer, pancreatic carcinoma, hepatocellular carcinoma, Hodgkin's disease, intraductal proliferative breast lesion, invasive ductal breast carcinoma, lung adenocarcinoma, nodal marginal zone B-cell lymphoma, and squamous cell carcinoma of the oral cavity (n = 1 each).

AE, adverse event; CI, confidence interval; EAIR, exposure-adjusted incidence rate; LTE, long-term extension; MACE, major adverse cardiovascular event; NMSC, nonmelanoma skin cancer; PY, person-years; QD, once daily; VTE, venous thromboembolism.

Results: PASI 75 response rates with continuous deucravacitinib treatment from Day 1 to 3 years

- PASI 75 response was sustained well from Week 52 (beginning of the POETYK LTE trial) through Week 148



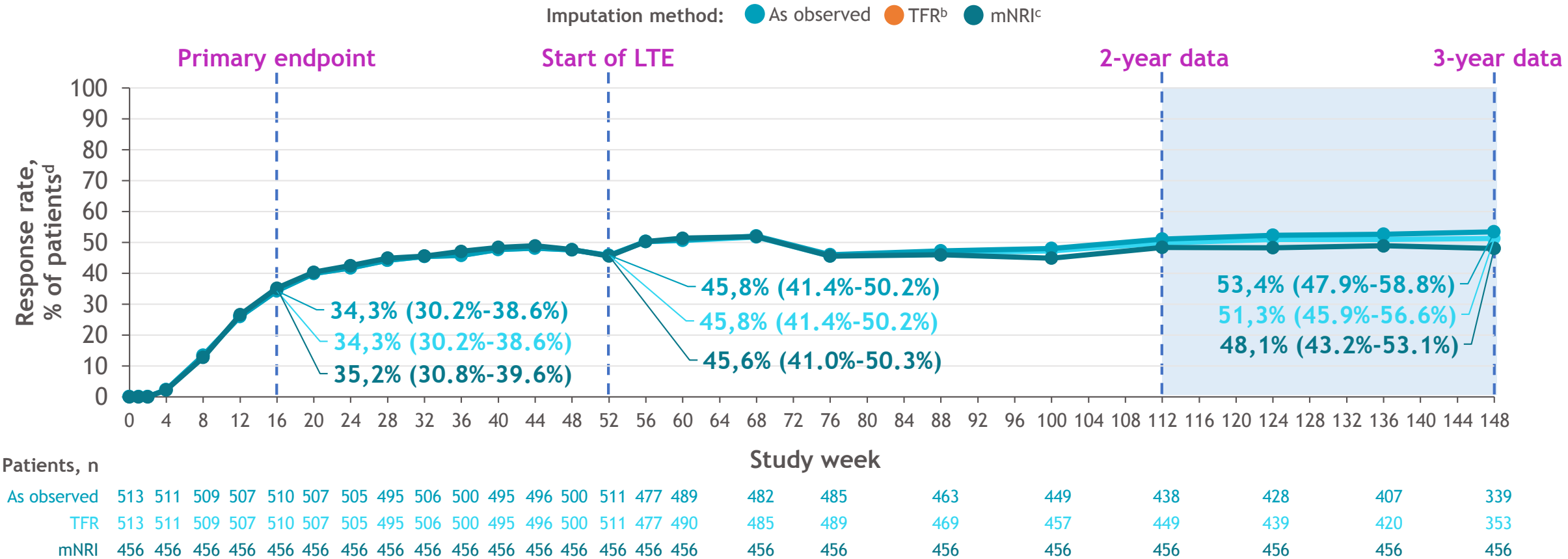
Patients, n																									
As observed	513	511	509	507	510	507	505	495	506	500	495	496	500	511	477	489	482	485	463	449	438	428	407	339
TFR	513	511	509	507	510	507	505	495	506	500	495	496	500	511	477	490	485	489	469	457	449	439	420	353
mNRI	456	456	456	456	456	456	456	456	456	456	456	456	456	456	456	456	456	456	456	456	456	456	456	456

[a]TFR analysis captures discontinuations coded as "lack of efficacy." [b]For mNRI analyses, if there are no missing data (ie, no imputed values in the dataset), 95% CI was obtained using the Clopper-Pearson method based on the observed data. [c]Data callouts represent the response rate (95% CI).

CI, confidence interval; LTE, long-term extension; mNRI, modified nonresponder imputation; PASI 75, ≥75% reduction from baseline in Psoriasis Area and Severity Index; TFR, treatment failure rules.

Results: PASI 90 response rates with continuous deucravacitinib treatment from Day 1 to 3 years

- PASI 90[a] response was sustained well from Week 52 (beginning of the POETYK LTE trial) through Week 148

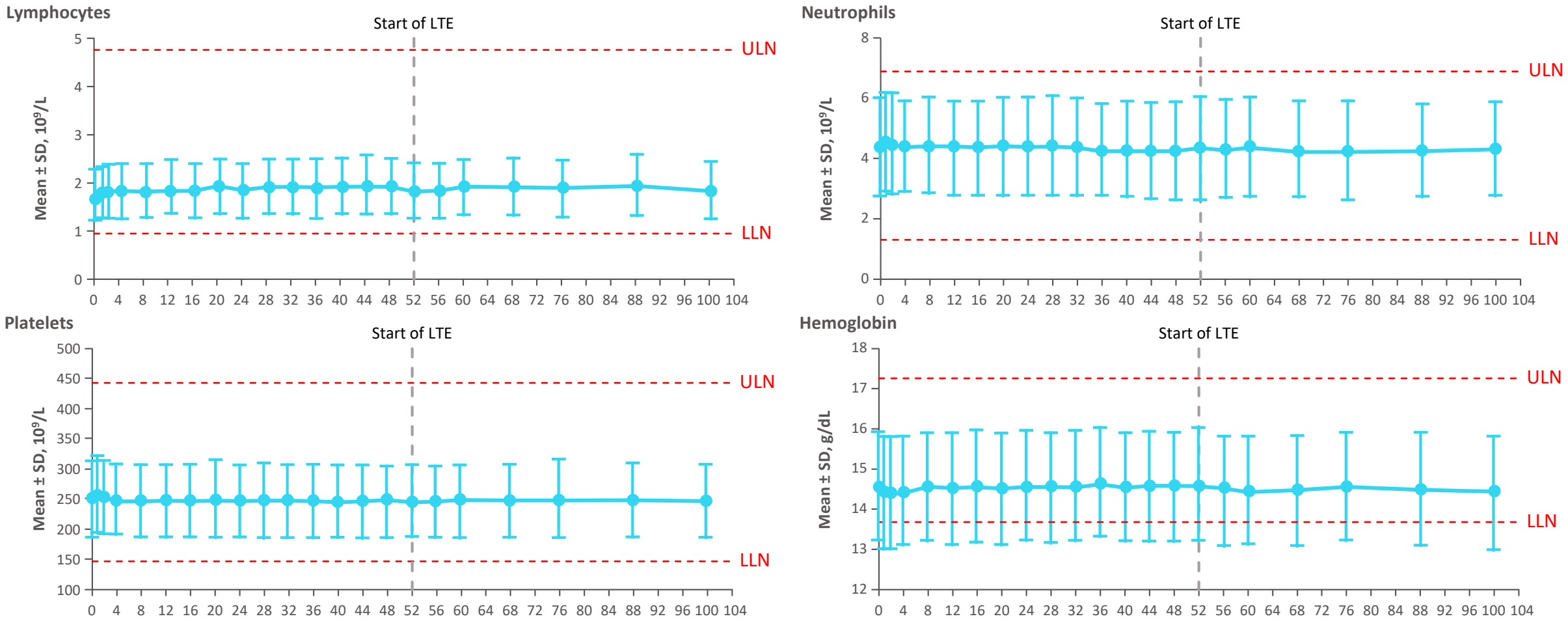


Patients, n																									
As observed	513	511	509	507	510	507	505	495	506	500	495	496	500	511	477	489	482	485	463	449	438	428	407	339
TFR	513	511	509	507	510	507	505	495	506	500	495	496	500	511	477	490	485	489	469	457	449	439	420	353
mNRI	456	456	456	456	456	456	456	456	456	456	456	456	456	456	456	456	456	456	456	456	456	456	456	456

[a]PASI 90 results were not estimable at Weeks 1 and 2 using mNRI. [b]TFR analysis captures discontinuations coded as "lack of efficacy." [c]For mNRI analyses, if there are no missing data (ie, no imputed values in the dataset), 95% CI was obtained using the Clopper-Pearson method based on the observed data. [d]Data callouts represent the response rate (95% CI).

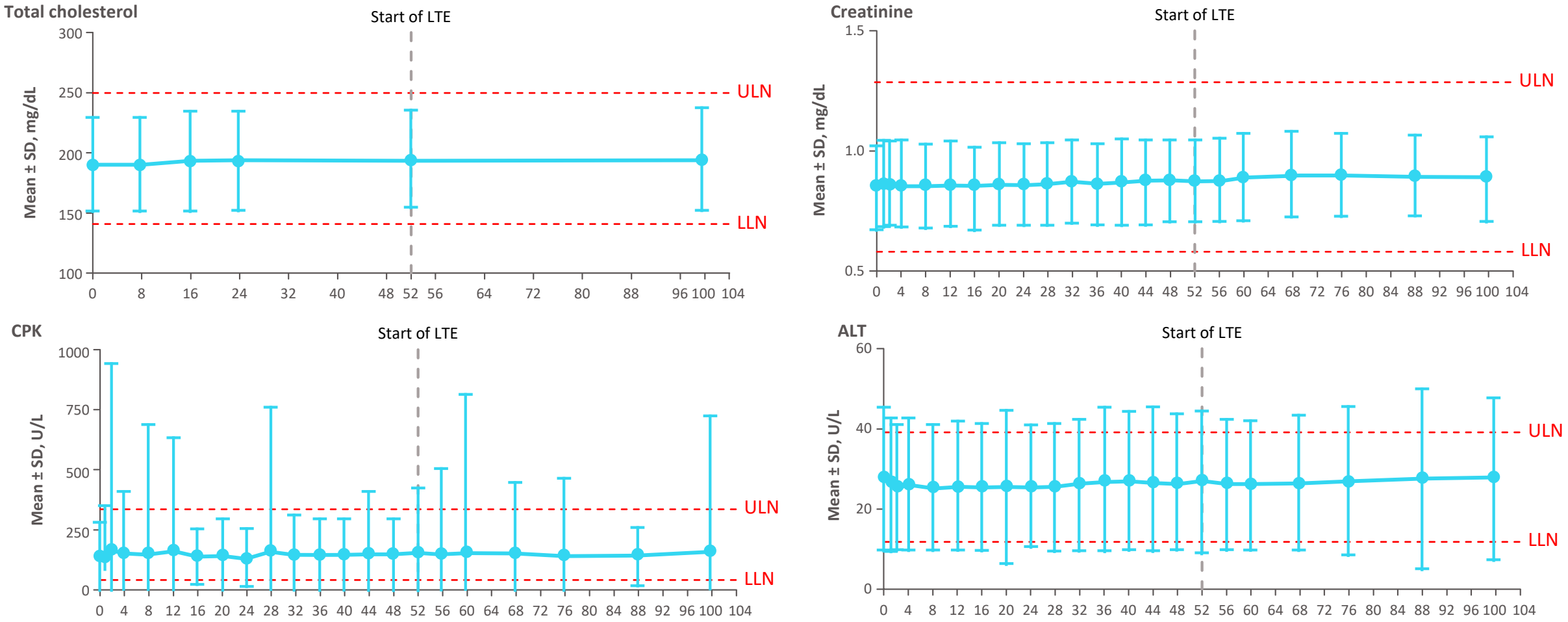
CI, confidence interval; LTE, long-term extension; mNRI, modified nonresponder imputation; PASI 90, ≥90% reduction from baseline in Psoriasis Area and Severity Index; TFR, treatment failure rules.

Changes in hematologic parameters over 2 years in patients receiving deucravacitinib[a]



Adapted with permission from Korman NJ.
[a]Includes patients who received ≥ 1 dose of deucravacitinib in POETYK PSO-1, PSO-2, and/or POETYK PSO-LTE through the data cutoff date of October 1, 2021.
LLN, lower limit of normal; LTE, long-term extension; SD, standard deviation; ULN, upper limit of normal.
Korman NJ et al. Poster presentation at EADV Annual Meeting; September 7–10, 2022; Milan, Italy. Poster P1481.

Changes in lipid and chemistry parameters over 2 years in patients receiving deucravacitinib[a]



Adapted with permission from Korman NJ.
[a]Includes patients who received ≥ 1 dose of deucravacitinib in POETYK PSO-1, PSO-2, and/or POETYK PSO-LTE through the data cutoff date of October 1, 2021.
CPK, creatine phosphokinase; LLN, lower limit of normal; LTE, long-term extension; SD, standard deviation; ULN, upper limit of normal.
Korman NJ et al. Poster presentation at EADV Annual Meeting; September 7–10, 2022; Milan, Italy. Poster P1481.

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https://doi.org/10.1080/14656566.2023.2211764

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DRUG EVALUATION

Deucravacitinib, a selective tyrosine kinase 2 inhibitor, for the treatment of moderate-to-severe plaque psoriasis

Marco Galluzzo [a,b], Laura Vellucci[a,b], Lorenzo Marcelli[a,b], Claudia Paganini[a,b], Luca Bianchi [a,b] and Marina Talamonti [b]

[a]Department of Systems Medicine, University of Rome "Tor Vergata", Rome, Italy; [b]Dermatology Unit, Fondazione Policlinico "Tor Vergata", Rome, Italy

… deucravacitinib has no impact on the so-called 'IL-6 inhibition signatures' obtained with known inhibitors of the IL-6 pathway, such as JAK1 inhibitors, that can increase cholesterol levels and decrease neutrophil counts.

Tabella 1: Elenco delle reazioni avverse

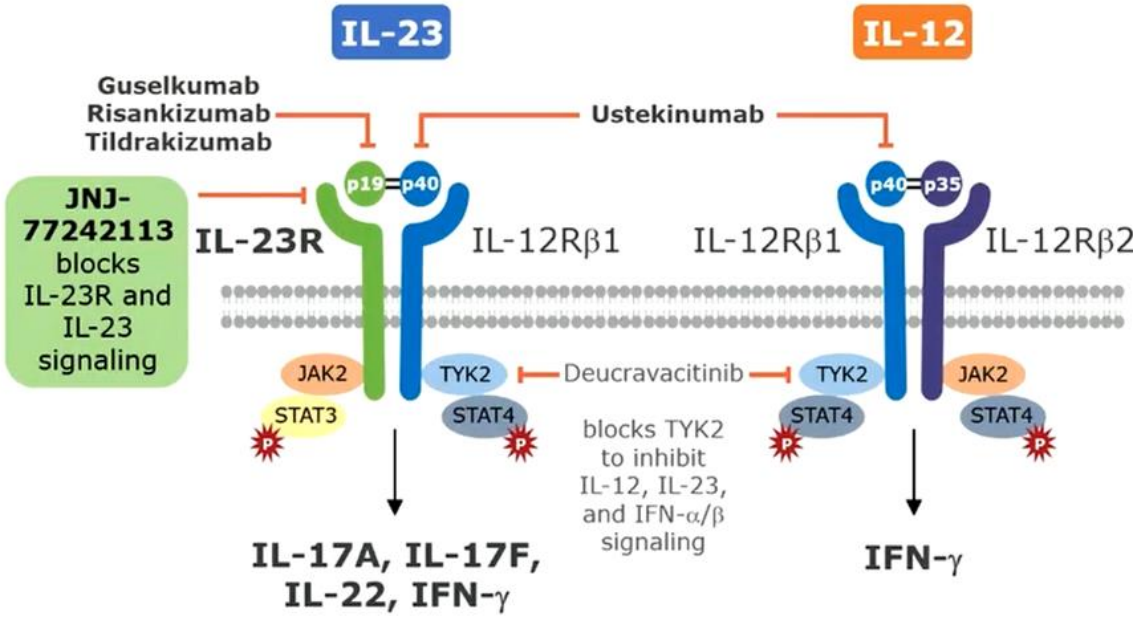
Classificazione per sistemi e organi	Frequenza	Reazione avversa
Infezioni ed infestazioni	Molto comune	Infezioni delle vie respiratorie superiori[a]
	Comune	Infezioni da Herpes simplex[b]
	Non comune	Herpes zoster
Patologie gastrointestinali	Comune	Ulcere orali[c]
Patologie della cute e del tessuto sottocutaneo	Comune	Eruzione cutanea acneiforme[d] Follicolite
Esami diagnostici	Comune	Creatinfosfochinasi ematica aumentata

[a] Le infezioni delle vie respiratorie superiori includono nasofaringite, infezione delle vie respiratorie superiori, infezione virale delle vie respiratorie superiori, faringite, sinusite, sinusite acuta, rinite, tonsillite, ascesso peritonsillare, laringite, tracheite e rinotracheite.
[b] Le infezioni da Herpes simplex includono herpes orale, herpes simplex, herpes genitale e infezioni da Herpes virus.
[c] Le ulcere orali includono ulcera aftosa, ulcerazione della bocca, ulcerazione della lingua e stomatite.
[d] L'eruzione cutanea acneiforme include acne, dermatite acneiforme, eruzione cutanea, rosacea, pustola, esantema pustoloso e papula.

RCP - Documento reso disponibile da AIFA il 01/09/2023

Catlett IM, Hu Y, Gao L, et al. Molecular and clinical effects of selective tyrosine kinase 2 inhibition with deucravacitinib in psoriasis. J Allergy Clin Immunol. 2022 Jun;149(6):2010–2020.e8. Epub 2021 Nov 10. DOI:10.1016/j.jaci.2021.11.001

Terapie emergenti in ambito Psoriasi – JNJ-2113



CD, Crohn's disease; IFN, interferon; PsA, psoriatic arthritis; PsO, psoriasis; UC, ulcerative colitis.

Pathway IL-23 rilevante in PsO, PsA, CD, UC

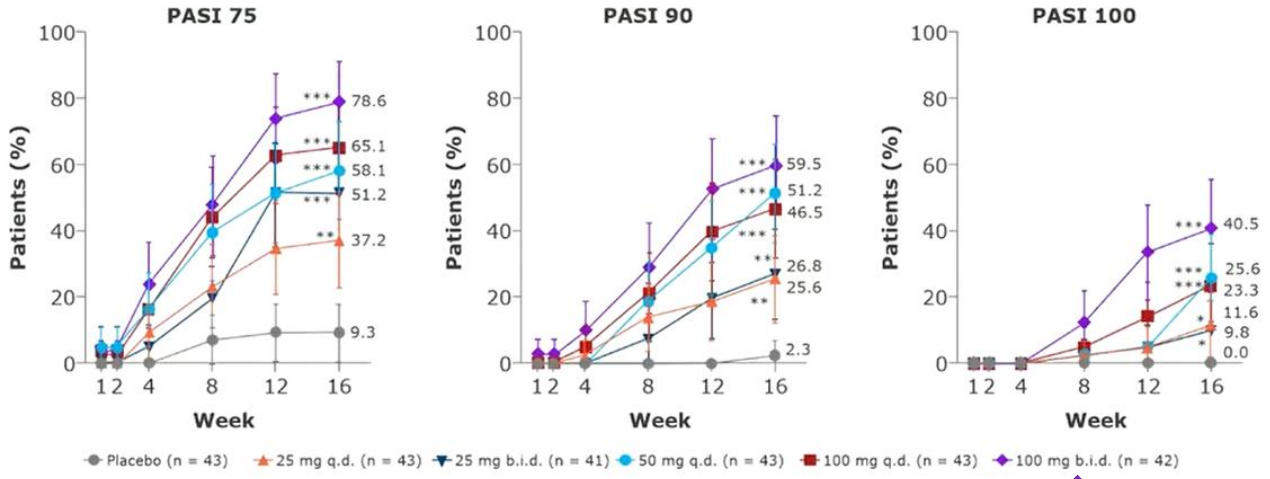
JNJ-2113:
Primo inibitore orale dell'IL23R che, con elevata selettività e potenza, blocca il segnale IL-23 e la produzione di citochine downstream.

April Armstrong, Division of Dermatology, University of California Los Angeles, CA, USA

Key Inclusion Criteria:
- 18 years of age and older
- PASI score ≥12
- IGA score ≥3
- BSA ≥10%

FRONTIER 1 (NCT05223868)[2]:

Studio di fase 2, randomizzato, PBO-controllato, dose-ranging, per la PsO moderata-severa.
255 pazienti
6 bracci:
PBO, 25 mg QD, 25 mg BID, 50 mg QD, 100 mg QD, 100 mg BID
Endpoint primario (NRI): PASI75 wk16
Endpoint secondari (NRI): PASI90/100, IGA 0/1, IGA 0, PSSD Symptom and Sign Scores
FRONTIER 2 (NCT05364554): LTE di ulteriori 40 settimane
Endpoint primario: PASI75 wk36



*Nominal p < 0.05 vs placebo.**Nominal p < 0.01 vs placebo. ***Nominal p < 0.001 vs placebo. p values are based on Cochran–Mantel–Haenszel (CMH) chi-square test stratified by baseline weight category (≤ 90 kg, > 90 kg). Patients who discontinued study agent due to lack of efficacy/worsening of PsO, or who initiated a prohibited PsO treatment were considered non-responders after the occurrence. Patients with missing data were considered non-responders.

1. Fourie A, et al., ISID 2023, Poster 1109. ISID: International Society Investigative Dermatology (May 2023, Tokyo, Japan); 2. Bissonette R, et al., Late breaking abstract WCD 2023

marco.galluzzo@uniroma2.it; marco.galluzzo@ptvonline.it

Ambulatorio dedicato alle malattie infiammatorie cronico cutanee: psoriasi, dermatite atopica

PDTA IMIDS