Η θέση του Apremilast για την επίτευξη των στόχων του ασθενή και του ιατρού στην Ψωριασική Αρθρίτιδα

ΔΗΜΗΤΡΟΥΛΑΣ ΘΕΟΔΩΡΟΣ

ΑΝΑΠΛΗΡΩΤΗΣ ΚΑΘΗΓΗΤΗΣ ΑΠΘ

Δ’ ΠΑΘΟΛΟΓΙΚΗ ΚΛΙΝΙΚΗ

ΙΠΠΟΚΡΑΤΕΙΟ ΝΟΣΟΚΟΜΕΙΟ ΘΕΣ/ΝΙΚΗΣ

Σύγκρουση Συμφερόντων

Παρούσα παρουσίαση: **Amgen**

Research/Educational support/grants

AbbVie, Boehringer Ingelheim, ELPEN, DEMO

Clinical trials (Phase II, III, IV)

AbbVie, Amgen, Boehringer Ingelheim, ELPEN, Lilly, Horizon Therapeutics, EMD Serono, Enorasis, Janssen

Consultancy fees, speaker fees, honoraria, advisory boards in the last 5 years

AbbVie, Amgen, Boehringer Ingelheim, ELPEN, Genesis Pharma, Janssen, Gilead,

Lilly, MSD, Novartis, Pfizer, SOBI, UCB, Vianex, Viatris

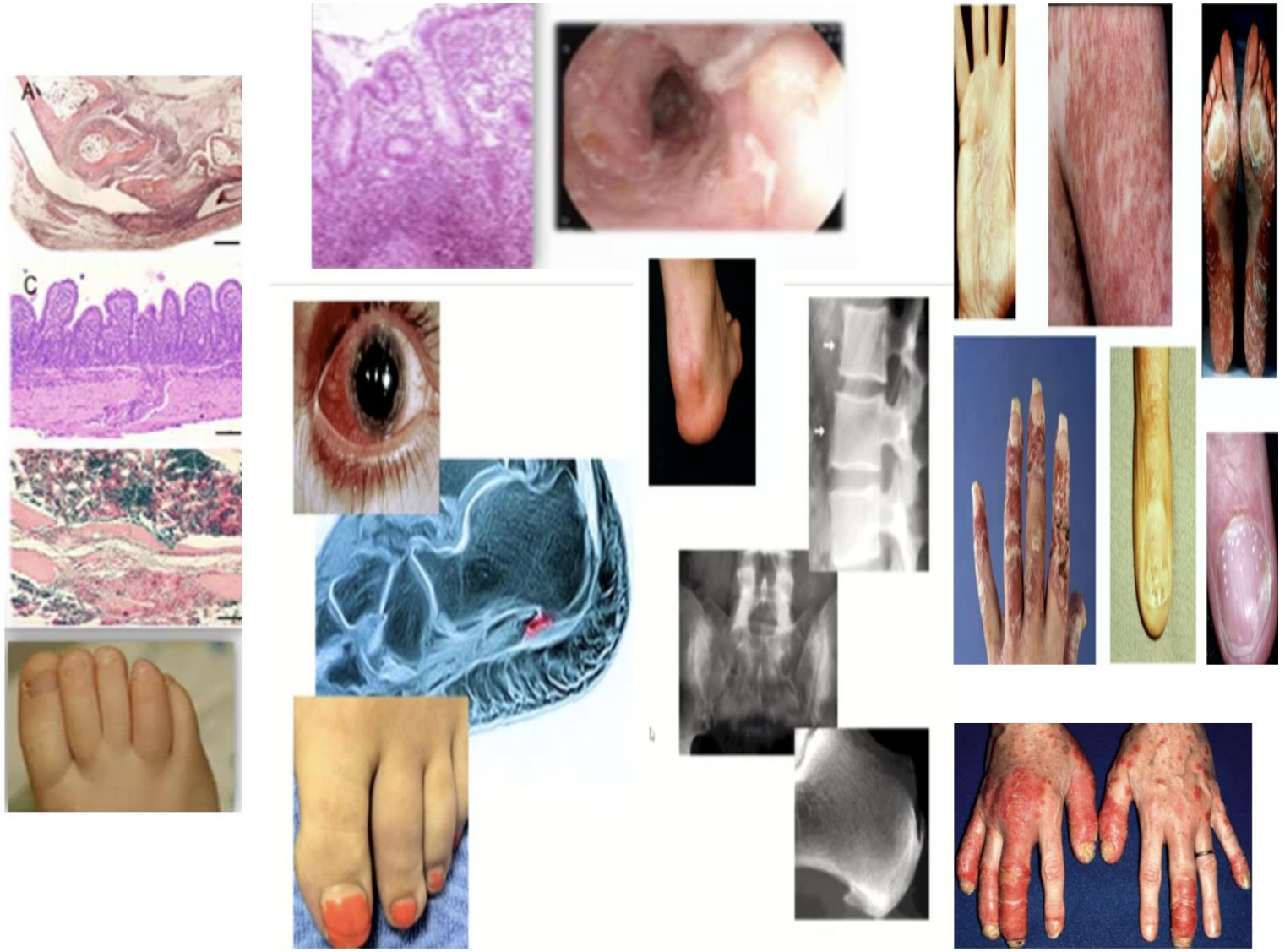
ΨΩΡΙΑΣΙΚΗ ΑΡΘΡΙΤΙΔΑ

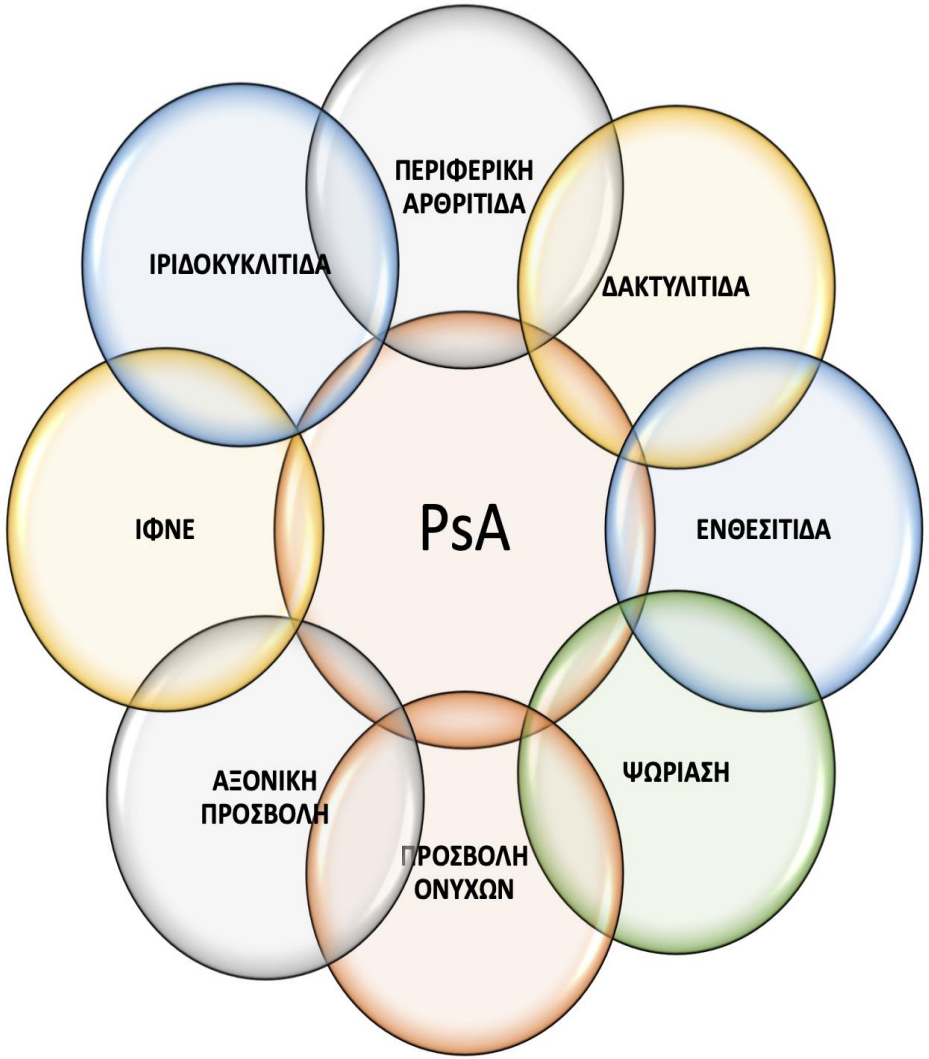
- Πόνος

- Δυσφορία

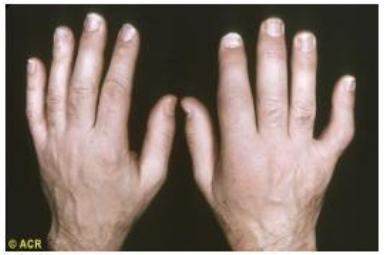
- Στρες

Ετερογένεια κλινικού φαινοτύπου στην Ψωριασική Αρθρίτιδα

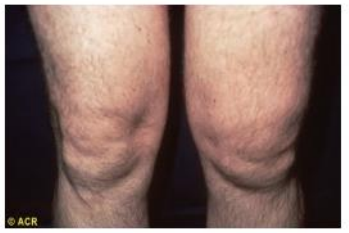




ΨΩΡΙΑΣΙΚΗ ΑΡΘΡΙΤΙΔΑ

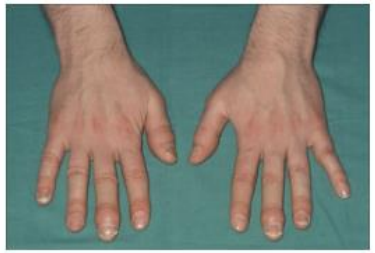


Πολυαρθρική προσβολή

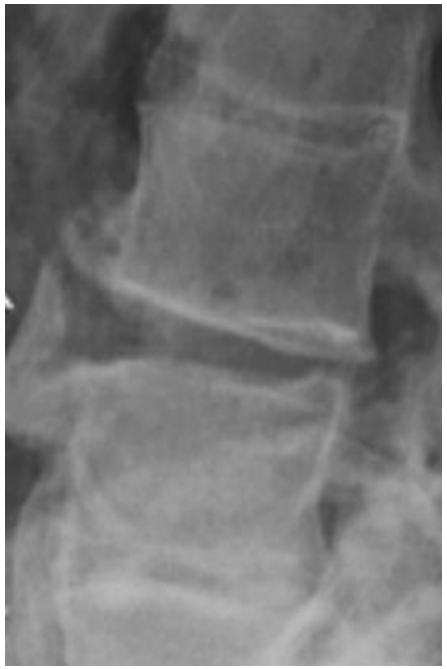


Ολιγοαρθρίτιτιδα

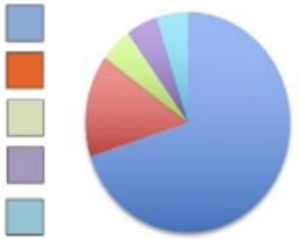
Τύπου ΟΑ – Προσβολή ΑΦΦ



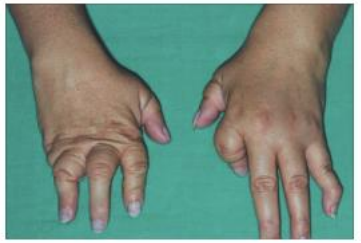
Αξονική προσβολή



1. asymmetrical oligoarthritis (>70%)
2. symmetrical polyarthritis (15%)
3. spondylitis (5%)
4. distal interphalangeal predominant (5%)
5. arthritis mutilans (<5%)



Καταστροφική (<1%)



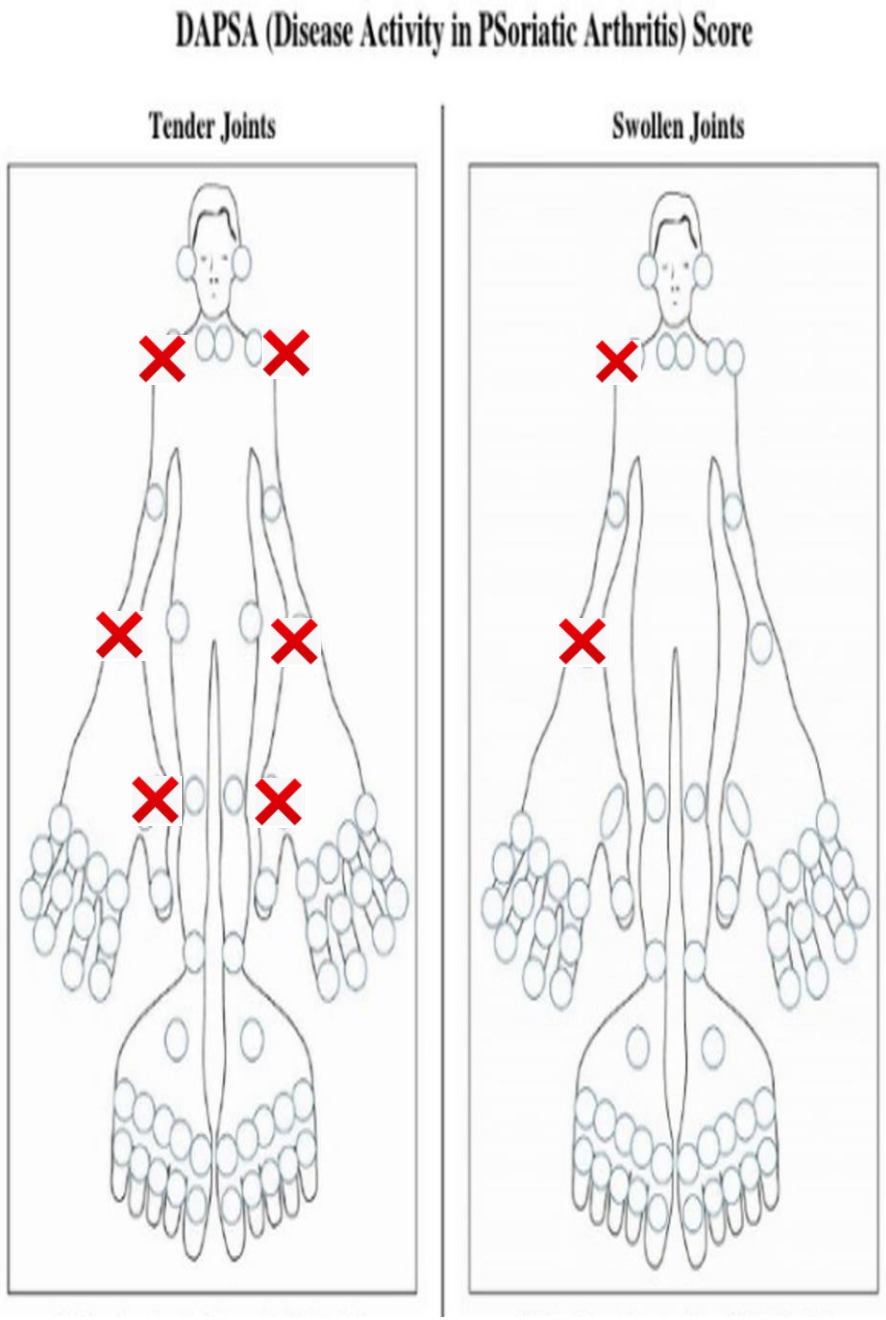
Case 1

Άνδρας 55 ετών (καθηγητής μέσης εκπαίδευσης). - 3/2016
Ιστορικό Ψωριασικής Αρθρίτιδας από 2 ετίας
Ολιγοαρθρίτιδα μεγάλων αρθρώσεων (κατ΄ώμων - πηχεοκαρπικές)
Ήπια δερματική ψωρίαση BSA (3-10%)

<u>Ατομικό Ιστορικό</u>
Υπέρταση
Σ/Δ τύπου ΙΙ
Χολόσταση αγνώστου αιτιολογίας (μέτρια↑ ALP, γGT)
Λιπώδης διήθηση ήπατος

Φαρμακευτική αγωγή
Amlopen/Ursofalk/Atorvastatin/Janumet

Case 1



- How active was your rheumatic disease on average during the last week?

not active 0 1 2 3 4 5 X 7 8 9 10 very active

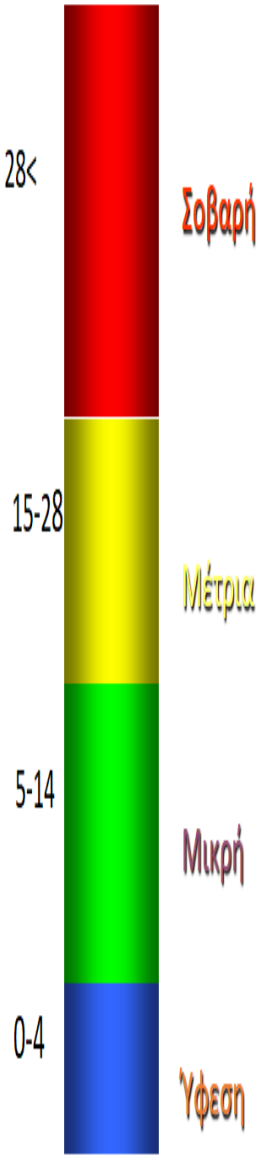
- How would you describe the overall level of joint pain during the last week?

none 0 1 2 3 4 X 6 7 8 9 10 very severe

Πρωϊνή δυσκαμψία > 30 min
Ψωριασικό εξάνθημα (BSA>3)
Δακτυλίτιδα (-)

DAPSA: 22,8
Επώδυνες: 6
Διογκωμένες:2
CRP: 3,8 (.6)mg/dl

DMARD naïve
Μέτρια ενεργότητα
Συννοσυρότητες



Case 1

Περιστασιακή χορήγηση κορτικοειδών (Celestone Chronodose)

Έναρξη MTX 15-20mg/week

Fillicine

Βελτίωση

κλινικών συμπτωμάτων

DAPSA: 6-8

CRP: 1,0 (.6)mg/dl

14 μήνες αργότερα

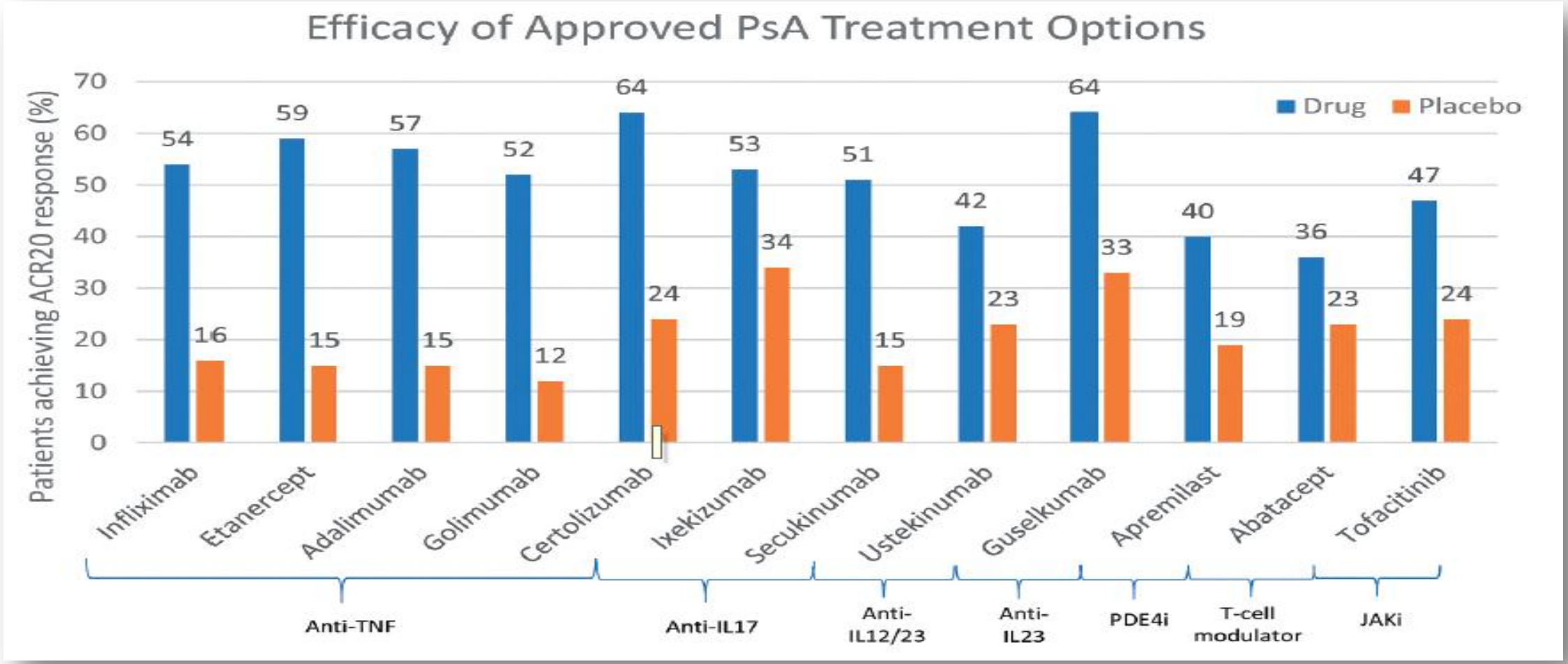
SGOT ↑ 80 U/LT
SGPT ↑ 60 U/LT
ALP ↑ 340 U/LT
γGT ↑105 U/LT

Διακοπή MTX για 5 μήνες
Ομαλοποίηση ηπατικής λειτουργίας

Επανεξέταση Ρευματολογικό Ιατρείο μετά από 7/12
Έξαρση νοσήματος
Αρθρίτιδα
Δυσκαμψία
CRP: 4,2 (.6)mg/dl

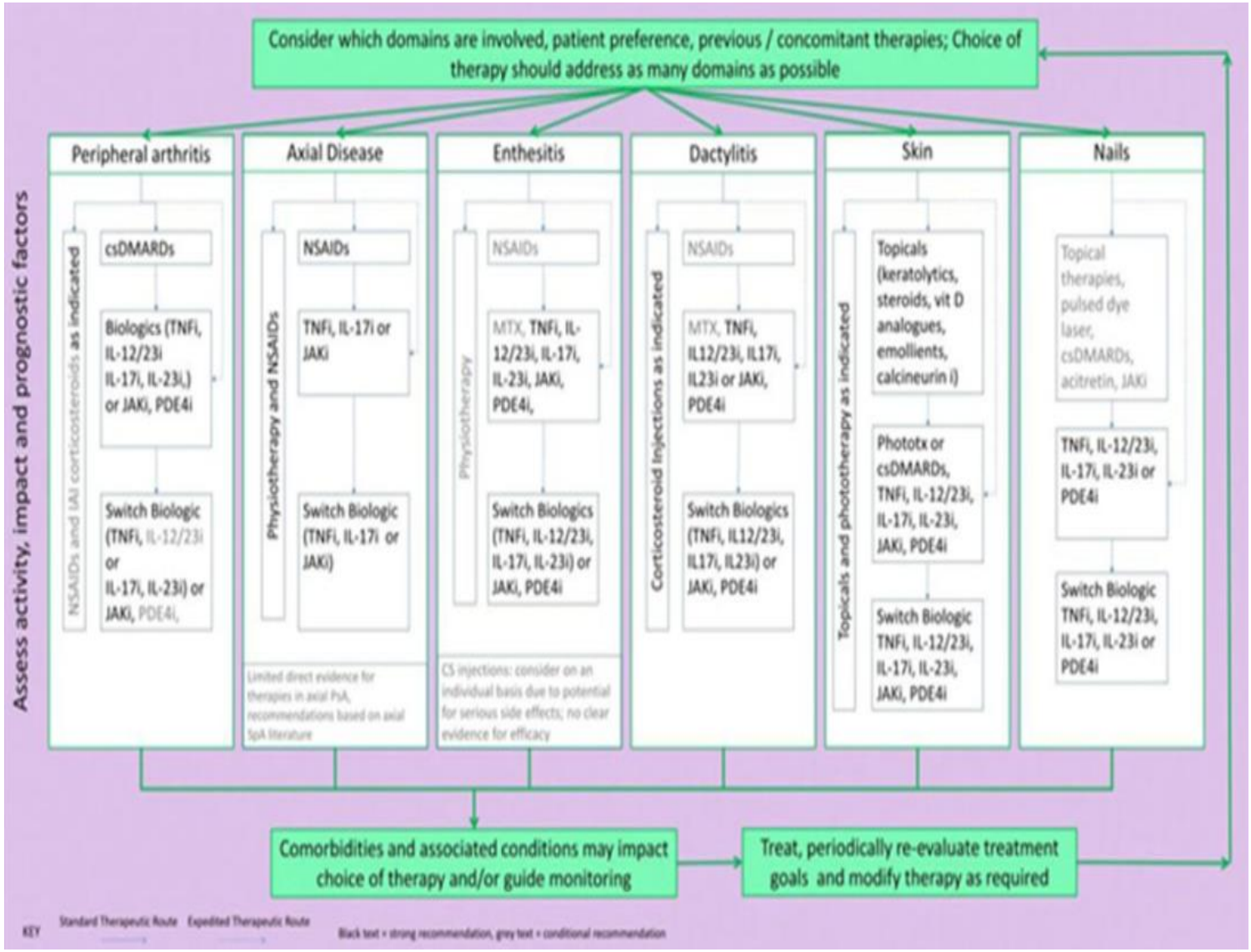
Επόμενο βήμα

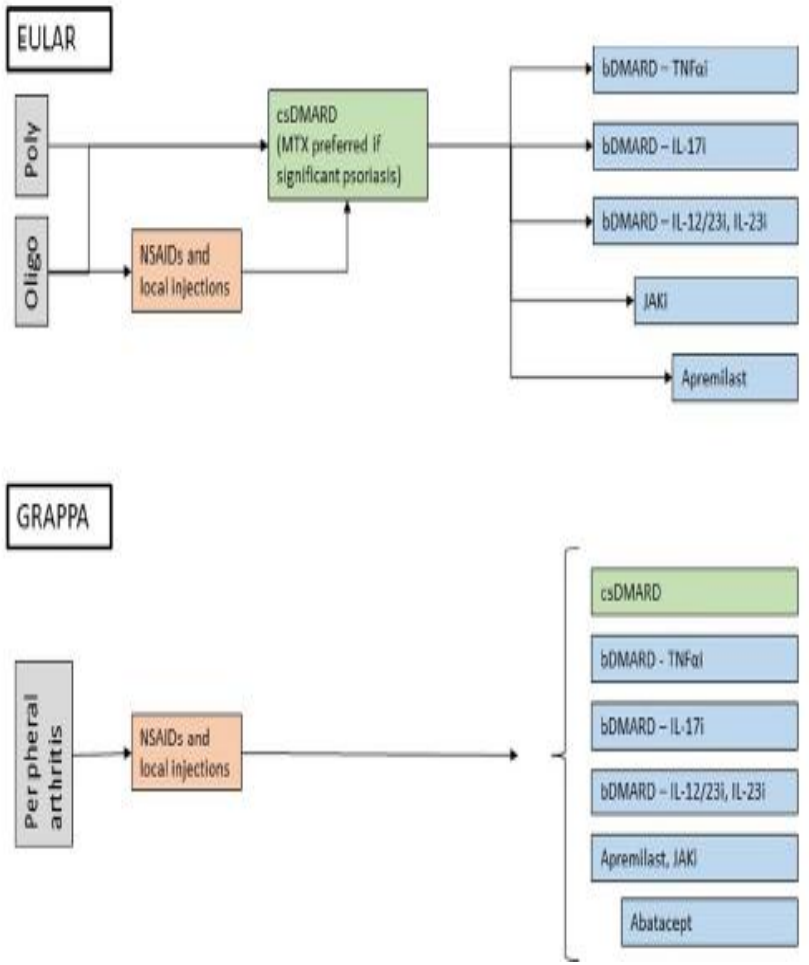
Αποτελεσματικότητα εγκεκριμένων βιολογικών θεραπειών στην ΨΑ
ACR20



Mohanakrishnan R et al, Expert Opin Biol Ther. 2022

THE GROUP FOR RESEARCH AND ASSESSMENT OF PSORIASIS AND PSORIATIC ARTHRITIS (GRAPPA) TREATMENT RECOMMENDATIONS 2021

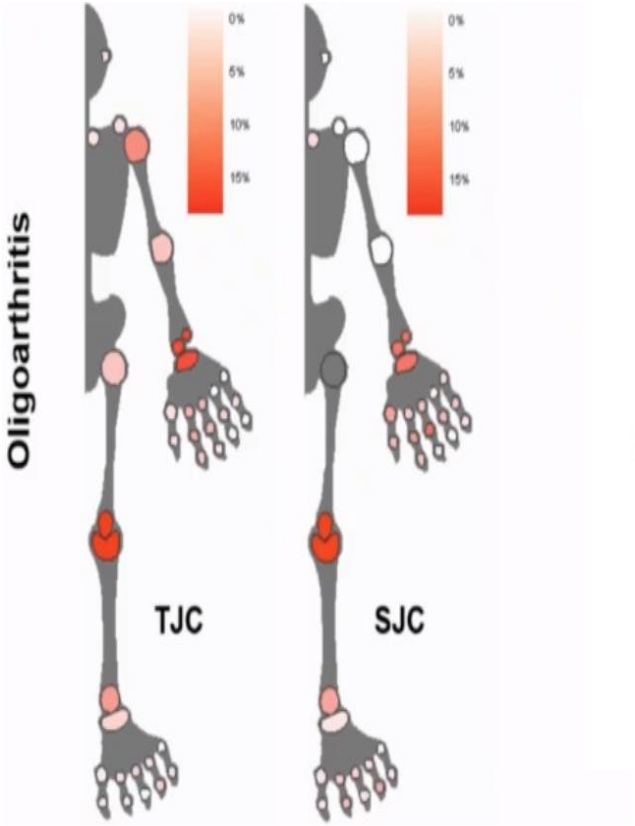


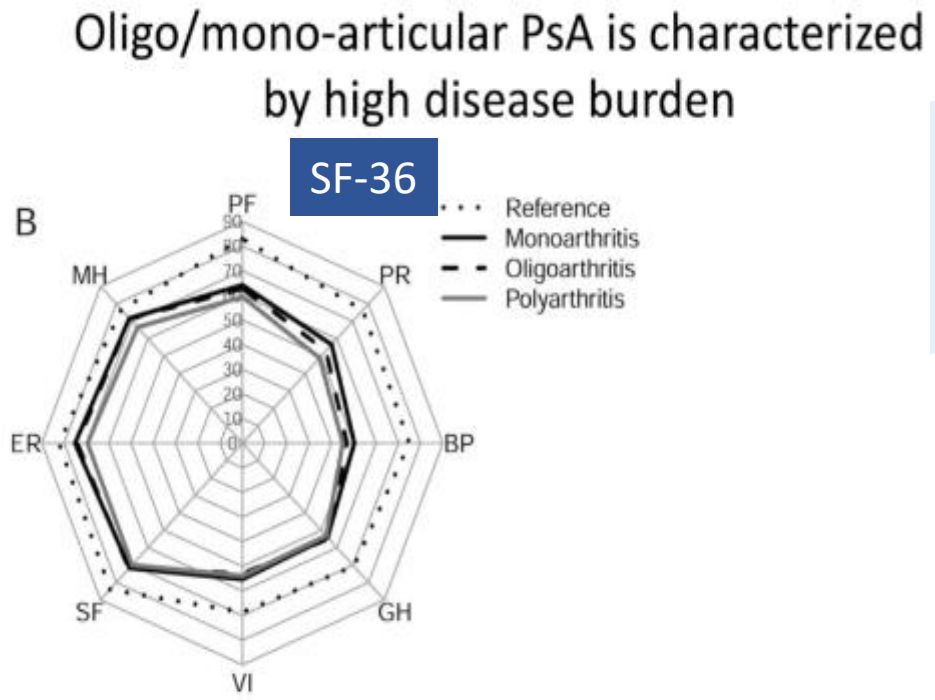


Coates L, et al. Nat Rev Rheumatol 2022

Coates L & Gossec L Joint Bone Spine 2022

Ολιγοαρθρική ψωριασική αρθρίτιδα – ένας διακριτός φαινότυπος [1-3]





Όλιγο/μόνο αρθρίτιδα

- ≤ 5 προσβεβλημένες αρθρώσεις
- 10-37%

Χαρακτηριστικά ολιγοαρθρίτιδας

- Μικρός αριθμός προσβεβλημένων αρθρώσεων (≤ 5 SJC και/ή TJC)[1-3]
- Ενθεσίτιδα (34% των ασθενών)[3]
- Δακτυλίτιδα (12% των ασθενών)[3]
- Υψηλό φορτίο συνοσηροτήτων[1]
- Μικρή αντιπροσώπευση στις κλινικές μελέτες

1. Ritchlin CT, et al. *N Engl J Med*. 2017;376:957-970; 2. Dhir V, et al. *Clin Rev Allergy Immunol*. 2013;44:141-148; 3. Coates LC, et al, Arthritis Rheum. 2013;65(6):1504–9 (Free to read on https://onlinelibrary.wiley.com/doi/epdf/10.1002/art.37939), 4 Wervers K et al J Rheum 2018 45(11) 1526-31

The Journal of Rheumatology 2021;48:693–7
doi:10.3899/jrheum.191209
First Release March 1 2021

The Journal of Rheumatology

Descriptive Comparisons of the Effect of Apremilast and Methotrexate Monotherapy in Oligoarticular Psoriatic Arthritis: The Corrona Psoriatic Arthritis/Spondyloarthritis Registry Results

Alexis Ogdie[1], Mei Liu[2], Meghan Glynn[2], Kelechi Emeanuru[2], Leslie R. Harrold[3], Sven Richter[4], Benoit Guerette[4], and Philip J. Mease[5]

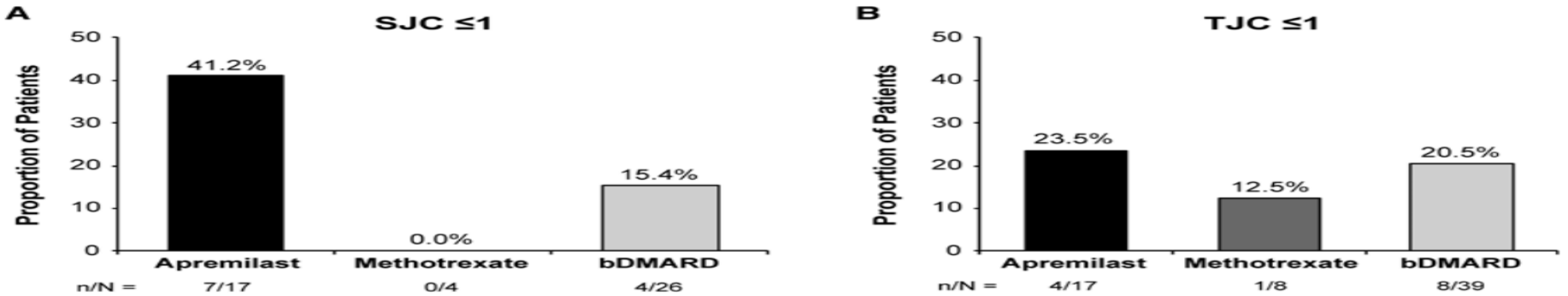


Figure 1. The proportions of patients with > 1 swollen joint or > 1 tender joint at baseline achieving (A) swollen joint count (SJC) ≤1 and (B) tender joint count (TJC) ≤1 at 6 months. bDMARD: biologic disease-modifying antirheumatic drug; n/N: number of responders/patients with sufficient data for evaluation.

N=34 N= 15 N=101

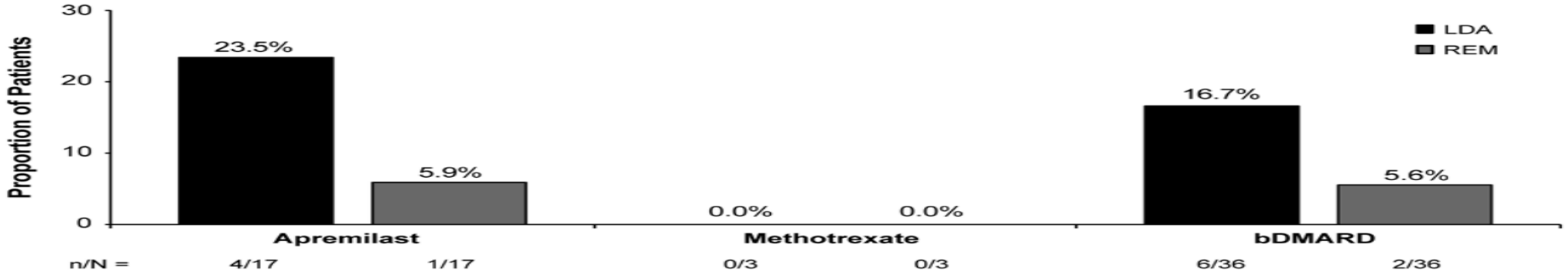


Figure 2. Achievement of low disease activity (LDA)/remission (REM). Proportions of patients in moderate or high Clinical Disease Activity Index for Psoriatic Arthritis (cDAPSA) categories at baseline achieving cDAPSA LDA or REM categories at 6 months. bDMARD: biologic disease-modifying antirheumatic drug; n/N: number of responders/patients with sufficient data for evaluation.

Moderate PsA allows good apremilast response

Pooled analyses from the Psoriatic Arthritis Long-term Assessment of Clinical Efficacy studies 1, 2, and 3 were performed. Probability analyses assessing the likelihood of achieving cDAPSA treatment targets by week 52

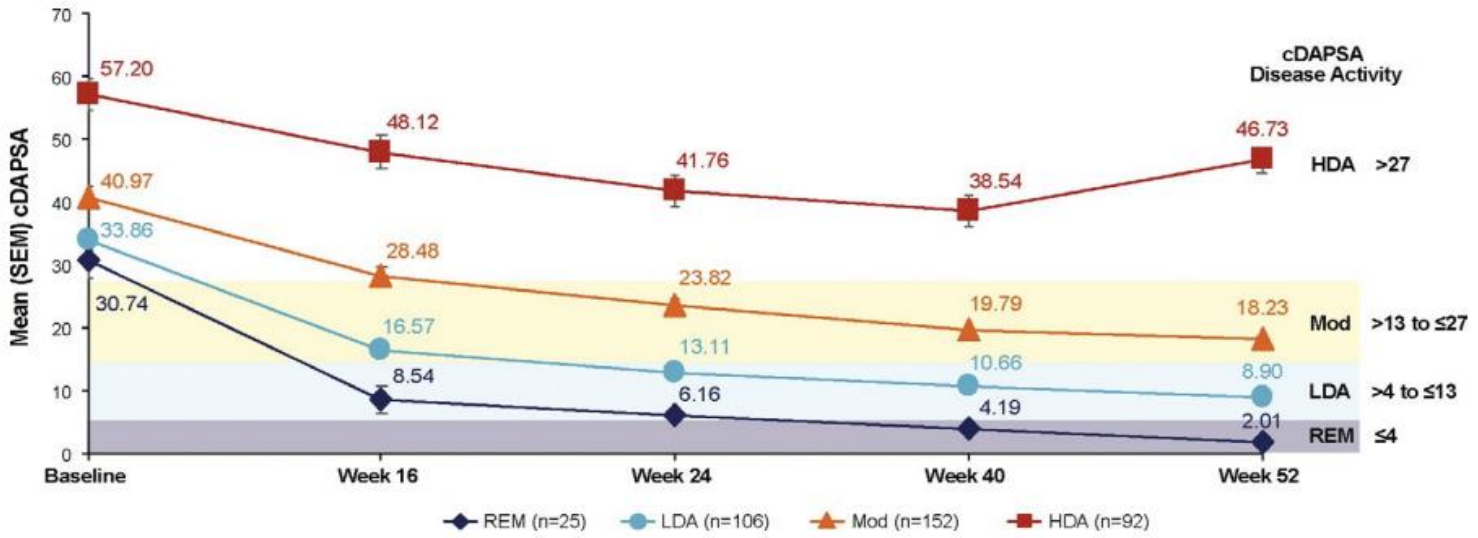


Figure 3. Disease activity through week 52 (n = 375) by Clinical Disease Activity Index for Psoriatic Arthritis (cDAPSA) (score range 0–154) category in patients receiving apremilast 30 mg twice a day from baseline, including patients randomized at baseline who had cDAPSA components available at week 52. Data are as observed. Remission (REM) score ≤4; low disease activity (LDA) score >4 to ≤13; moderate disease activity (Mod) score >13 to ≤27; and high disease activity (HDA) score >27. Error bars indicate the SEM.

Mease P et al Arthritis Care Res (Hoboken). 2020 Jun;72(6):814-821.

Apremilast: Μείωση του αριθμού των επώδυνων και διογκωμένων αρθρώσεων

Τελευταία δεδομένα των μελετών καθημερινής κλινικής πράξης

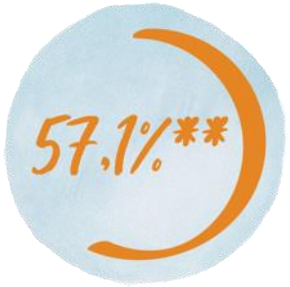
APs: Artritis Psoriásica.

1. Chandran V, et al. Ann Rheum Dis. 2021;80(Suppl 1):1313-4. 2. De Vlam K, et al. Adv Ther. 2022;39:1055-67. 3. Bos R, et al. Ann Rheum Dis. 2022;81(Suppl1):1565-6. 4. Wollenhaupt J, et al. EULAR 2020. Poster FRI0365.
5. Añón Oñate I, et al. Ann Rheum Dis 2020;79(Supplement 1):1657.

Apremilast: Μείωση του αριθμού των επώδυνων και διογκωμένων αρθρώσεων

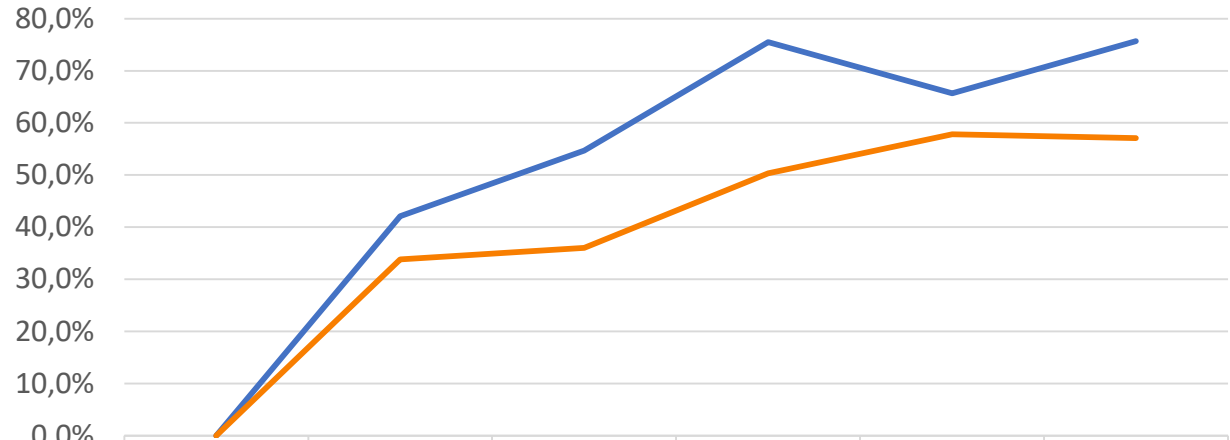
LAPIS-PsA

Μέση βελτίωση στις **διογκωμένες αρθρώσεις** στους 13 μήνες



Μέση βελτίωση στις **επώδυνες αρθρώσεις** στους 13 μήνες

% Μέσης βελτίωσης των επώδυνων (TJC) και διογκωμένων (SJC) αρθρώσεων (CI 95%)



	Αρχική εξέταση	Επίσκεψη 1	Επίσκεψη 2	Επίσκεψη 3	Επίσκεψη 4	Επίσκεψη 5
SJC	0,0%	42,1%	54,7%	75,5%	65,7%	75,7%
TJC	0,0%	33,8%	36,0%	50,3%	57,8%	57,1%

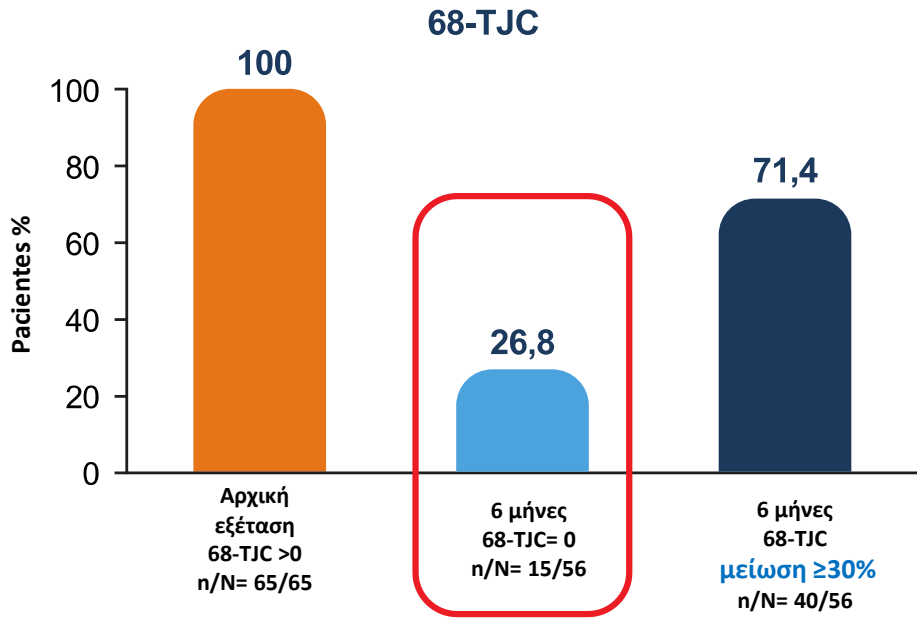
SJC TJC

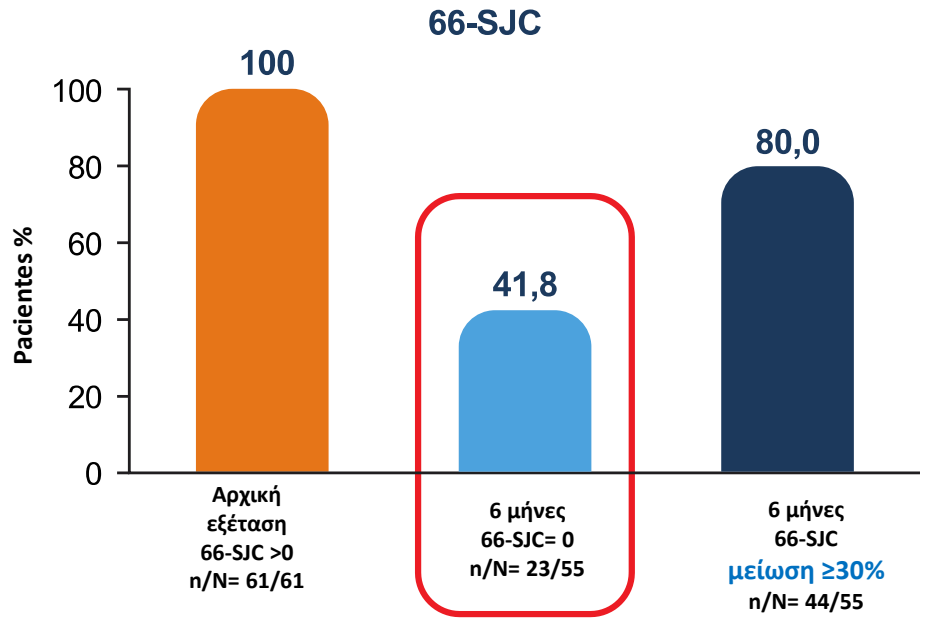
Wollenhaupt J, et al. EULAR 2020. Poster FRI0365

Apremilast: Μείωση του αριθμού των επώδυνων και διογκωμένων αρθρώσεων

APOLO

Στο **41,8%** (23/55) και στο **26,8%** (15/56) των ασθενών με SJC >0 και TJC >0 στην αρχική εξέταση αντίστοιχα, πέτυχαν **SJC=0 kai TJC=0** στους **6 μήνες θεραπείας με το apremilast**





De Vlam K, et al. Adv Ther. 2022;39:1055-67.

Apremilast

Βελτίωση της εξέλιξης της νόσου

RWE

Añón Oñate I, et al.

Με το apremilast οι ασθενείς πέτυχαν μία **σημαντική μείωση της ενεργότητας της νόσου**

Ύφεση κατά DAPSA

των ασθενών **πέτυχαν ύφεση** στους 18 μήνες#

a los 18 meses

Χαμηλή ενεργότητα κατά DAPSA

των ασθενών **πέτυχαν χαμηλή ενεργότητα νόσου** στους 18 μήνες#

a los 18 meses

Χαρακτηριστικά ασθενών με ΨΑ που χρειάστηκαν apremilast

Ασθενείς με ΨΑ	Αρχική εξέταση	6 μήνες	12 μήνες	18 μήνες	p
TJC	3,3 ± 2,0	1,2 ± 2,3	1,1 ± 1,6	0,7 ± 1,1	*p= 0,002
SJC	2,4 ± 1,6	0,4 ± 0,9	1,0 ± 2,0	0,3 ± 1,0	*p= 0,001
PCR	6,8 ± 6,3	3,5 ± 3,8	3,4 ± 3,9	2,7 ± 4,1	p= 0,062
DAPSA	21,1 ± 5,6	5,6 ± 7,2	6,5 ± 8,5	2,9 ± 4,1	*p= 0,000
MASES	1 ± 1,4	0,1 ± 0,5	0 ± 0	0 ± 0	p= 0,16

#από τους 42 ασθενείς με ΨΑ. *στατιστικά σημαντικές τιμές.

Añón Oñate I, et al. Ann Rheum Dis 2020;79(Supplement 1):1657.

A non-interventional prospective observational study assessing **APR**emilast in ps**O**riatic **A**rthritis in real-life **C**linical practice in Greek **H**ealthcare environment

APROACH

Rheumatology International
https://doi.org/10.1007/s00296-022-05269-z

Rheumatology
INTERNATIONAL

OBSERVATIONAL RESEARCH

Check for updates

Apremilast for biologic-naïve, peripheral psoriatic arthritis, including patients with early disease: results from the APROACH observational prospective study

Petros P. Sfikakis[1,2] · Dimitrios Vassilopoulos[2,3] · Gkikas Katsifis[4] · Georgios Vosvotekas[5] · Theodoros Dimitroulas[6] · Prodromos Sidiropoulos[7] · Periklis Vounotrypidis[8] · Dimitrios P. Bogdanos[9] · Athanasios I. Georgountzos[10] · Andreas G. Bounas[11] · Panagiotis Georgiou[12] · Souzana Gazi[13] · Evangelia Kataxaki[14] · Stamatis-Nick Liossis[15] · Evangelos Theodorou[16] · Charalampos Papagoras[17] · Evangelos Theotikos[18] · Panayiotis Vlachoyiannopoulos[2,19] · Paraskevi V. Voulgari[20] · Angeliki Kekki[21] · Nikolaos Antonakopoulos[21] · Dimitrios T. Boumpas[2,22]

Patients' Geographic Distribution

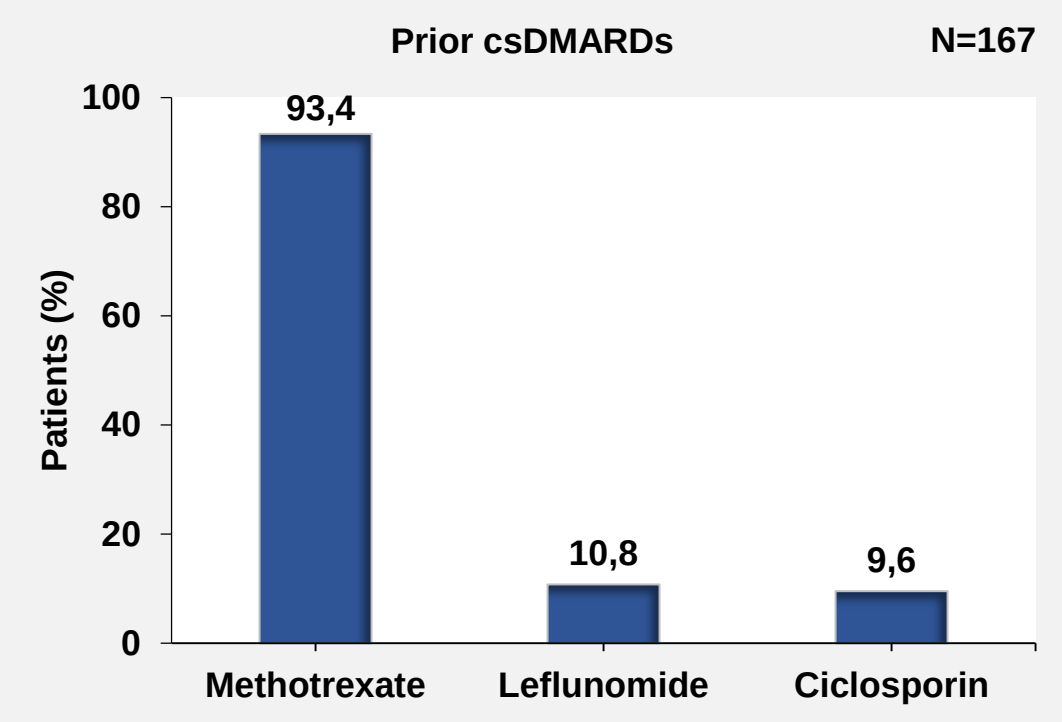
	Region	Sites	Patients analyzed	
			N	(%)
1	Attica	10	93	55.7
2	Central Macedonia	3	34	20.4
3	Western Greece	3	17	10.2
4	Crete	1	10	6.0
5	Thessaly	1	9	5.4
6	Eastern Macedonia and Thrace	1	3	1.8
7	Epirus	1	1	0.6
	Total	**20**	**167**	**100.0**

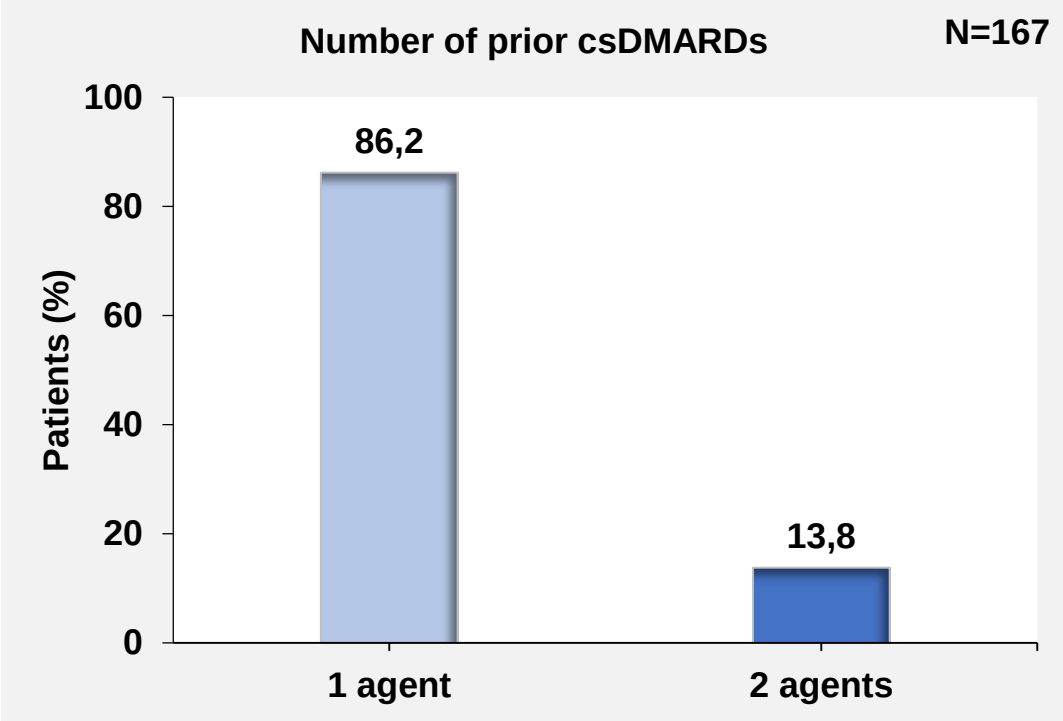
Study Population

- Number of enrolled patients: **170**
- Number of analyzed patients: **167**
- Main inclusion criteria:
  - Adult patients with active peripheral PsA, **biologic-naïve**,
  - who have been intolerant to a prior DMARD therapy, or who have had an inadequate response (to at least one DMARD and **within the first 12 months** of treatment), and
  - who have been prescribed treatment with **apremilast (Otezla®) for PsA**, prior to signed Informed Consent and for whom, if treatment has started, **≤ 1 week has elapsed from treatment initiation** to obtaining the signed Informed Consent
- Main exclusion criterion:
  - Patients who have a history of exposure to biologic treatment and/or to tofacitinib in PsA

Prior medications for PsA/psoriasis at baseline

- Prior therapies for PsA/psoriasis included csDMARDs in all 167 patients.
- Therapies other than DMARDs had been administered to 59.3% of the patients, comprising oral NSAIDs (34.7%), topical treatments (16.8%), systemic steroids (14.4%), folic acid (7.8%), intra-articular steroid injections (1.8%), photo(chemo)therapy (0.6%), acitretin (0.6%), and pregabalin (0.6%).

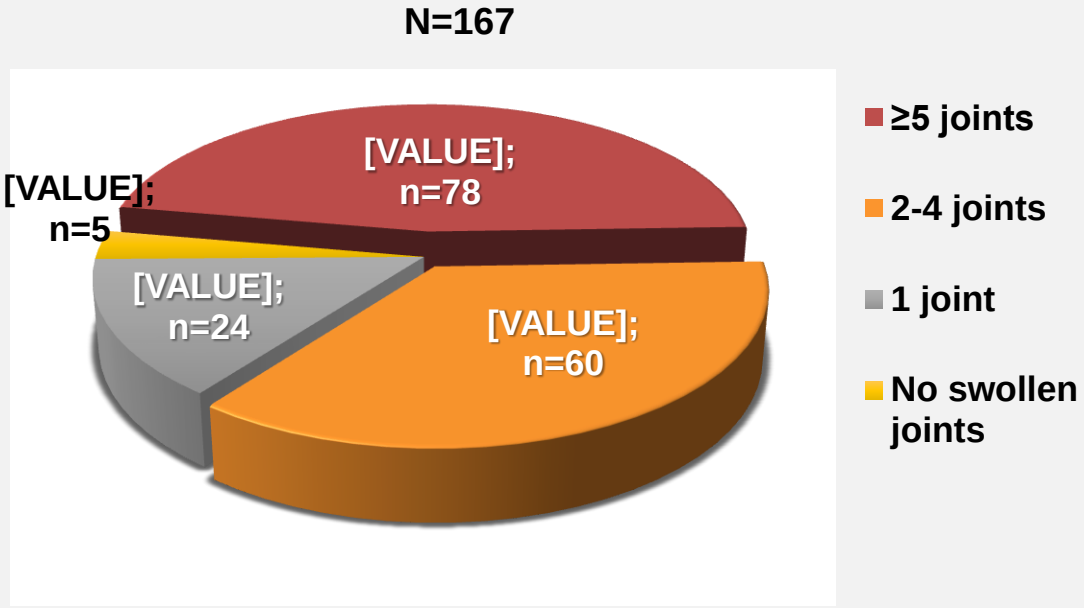




csDMARD, conventional synthetic disease-modifying antirheumatic drug

Disease characteristics at baseline

Distribution based on **66-SJC** count at baseline

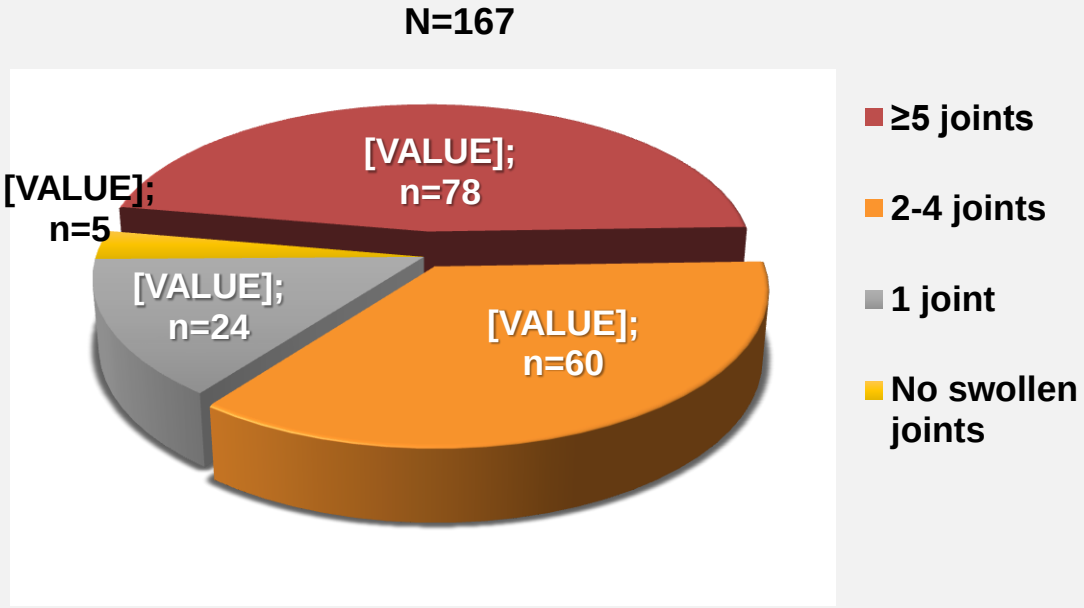


DAPSA score, median (IQR)	132	24.4 (18.8–31.8)
cDAPSA score, median (IQR)	167	22.0 (16.0–29.0)
Number of swollen joints, median (IQR)	167	4.0 (2.0–8.0)
Number of tender joints, median (IQR)	167	5.0 (2.0–9.0)
CRP levels, mg/dL, median (IQR)	132	1.0 (0.5–3.0)
Active skin psoriasis (BSA>0%), *n* (%)	167	146 (87.4)
Nail involvement, *n* (%)	162	61 (37.7)
Enthesitis, *n* (%)	163	50 (30.7)
Dactylitis, *n* (%)	161	20 (12.4)

- ✓ Early disease
- ✓ Biologic naïve
- ✓ Moderate activity
- ✓ Oligoarticular disease

Disease characteristics at baseline

Distribution based on **66-SJC** count at baseline

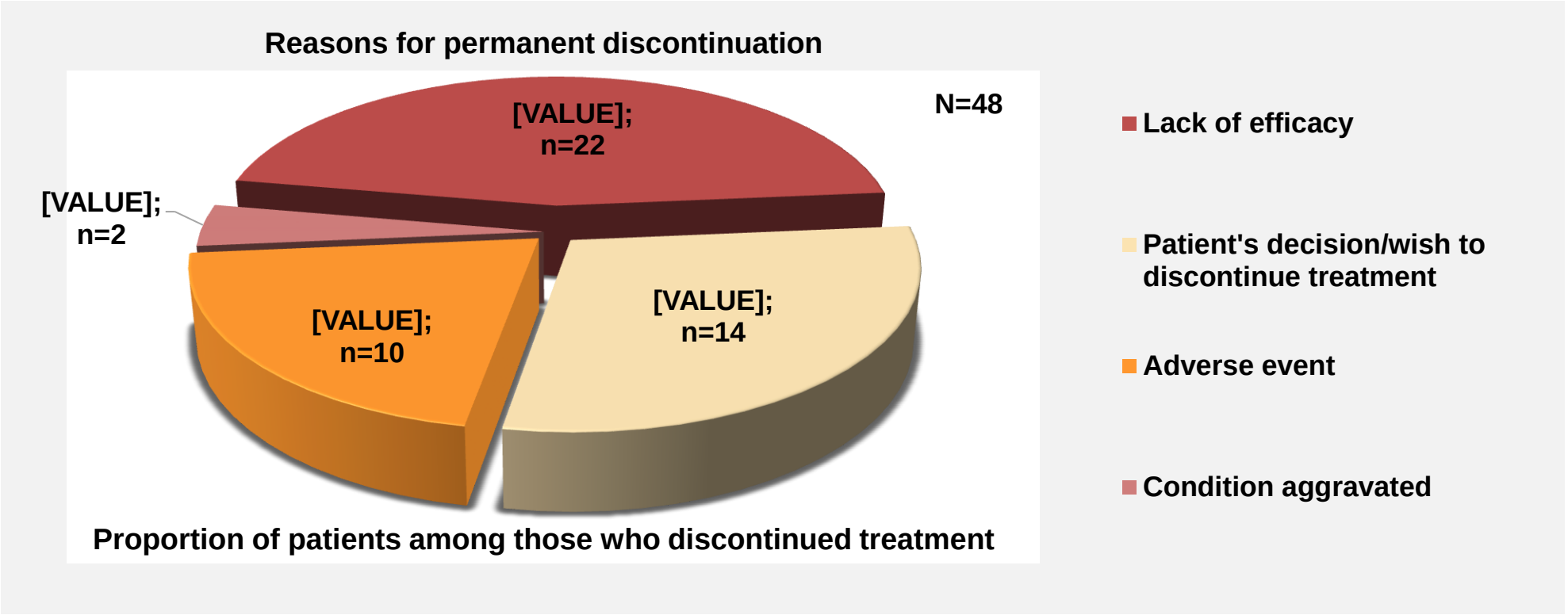


DAPSA score, median (IQR)	132	24.4 (18.8–31.8)
cDAPSA score, median (IQR)	167	22.0 (16.0–29.0)
Number of swollen joints, median (IQR)	167	4.0 (2.0–8.0)
Number of tender joints, median (IQR)	167	5.0 (2.0–9.0)
CRP levels, mg/dL, median (IQR)	132	1.0 (0.5–3.0)
Active skin psoriasis (BSA>0%), *n* (%)	167	146 (87.4)
Nail involvement, *n* (%)	162	61 (37.7)
Enthesitis, *n* (%)	163	50 (30.7)
Dactylitis, *n* (%)	161	20 (12.4)

- ✓ Early disease
- ✓ Biologic naïve
- ✓ Moderate activity
- ✓ Oligoarticular disease

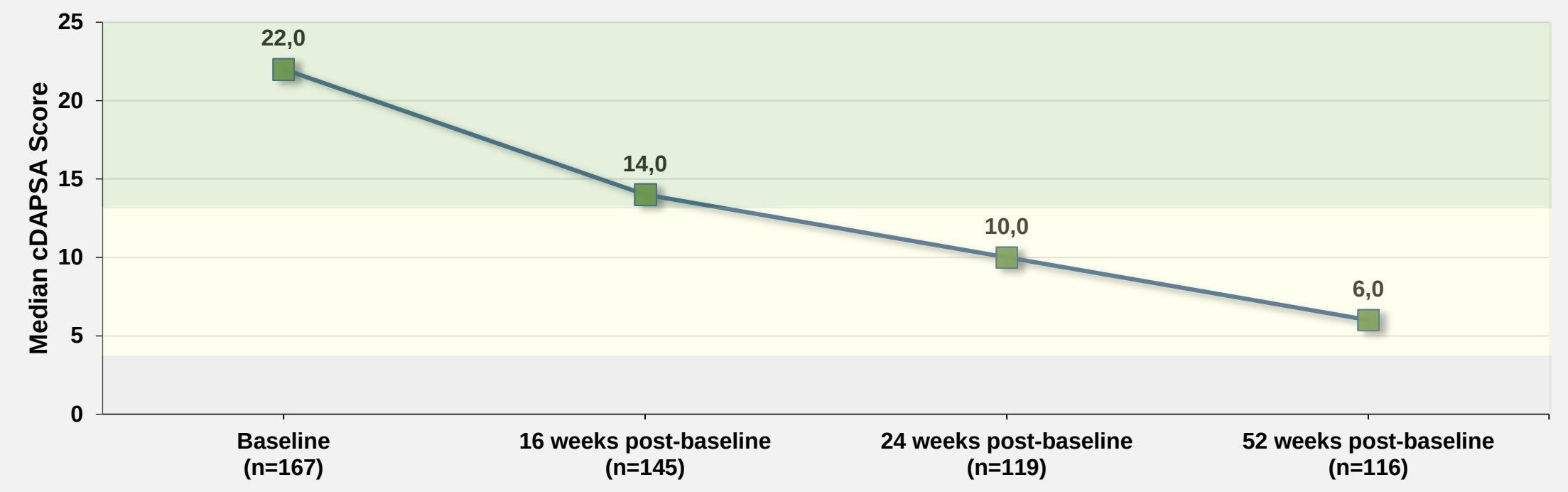
Apremilast permanent discontinuation

- **30.4%** (48/158) of the patients permanently discontinued apremilast treatment.



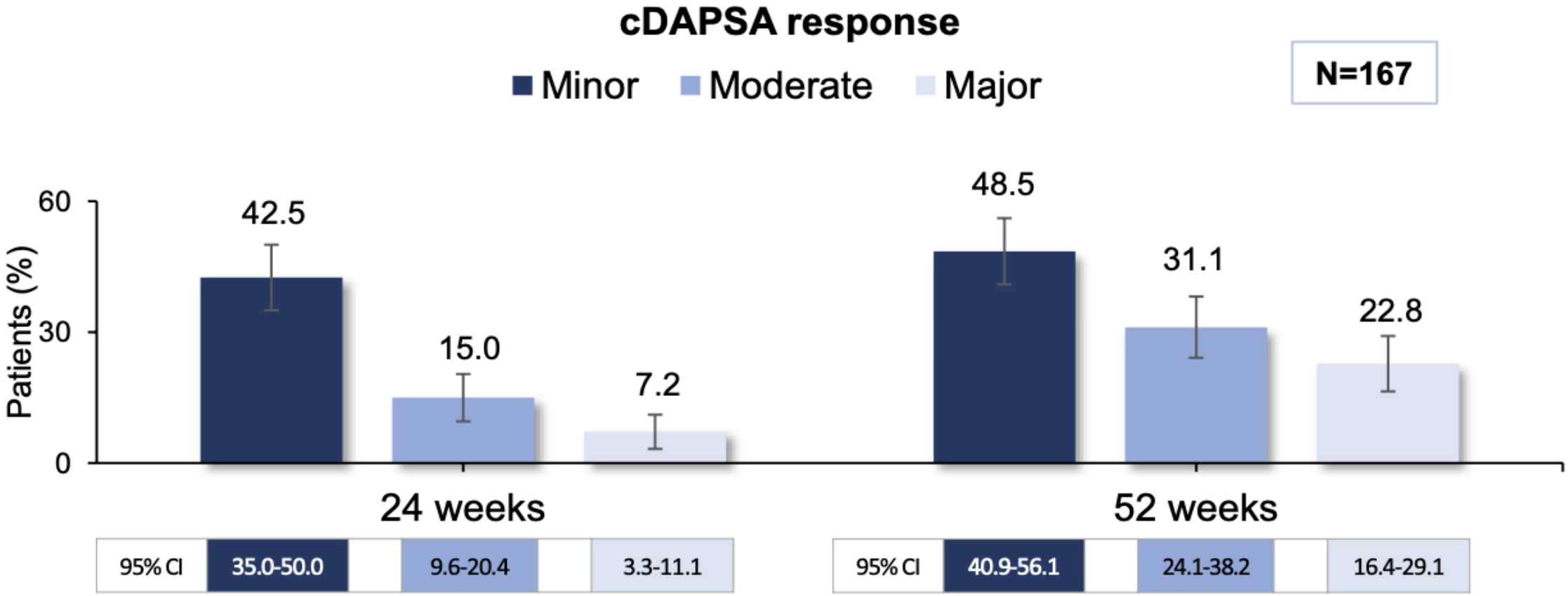
cDAPSA score at baseline, 16, 24, and 52 weeks post-baseline

- The median (IQR) cDAPSA scores were **22.0** (16.0-29.0), **14.0** (9.0-18.0), **10.0** (6.0-15.0) and **6.0** (2.0-12.0) at **baseline**, **16**, **24** and **52 weeks** post-baseline, respectively.



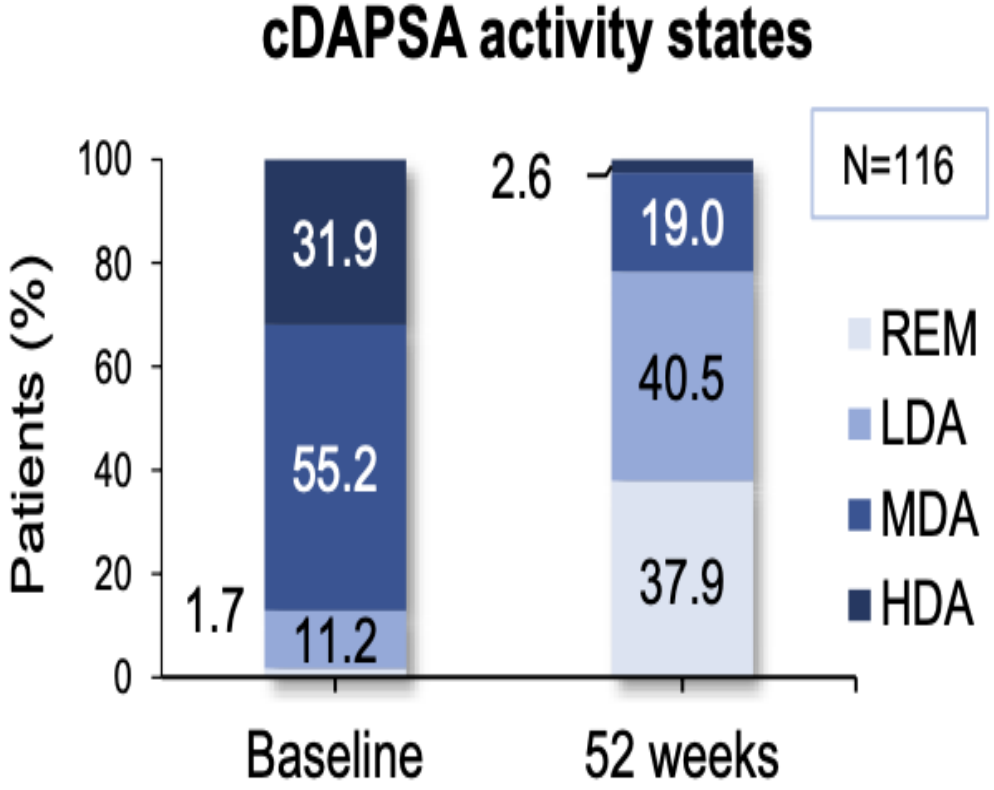
cDAPSA, clinical disease activity in psoriatic arthritis

cDAPSA response in 24, and 52 weeks post-baseline

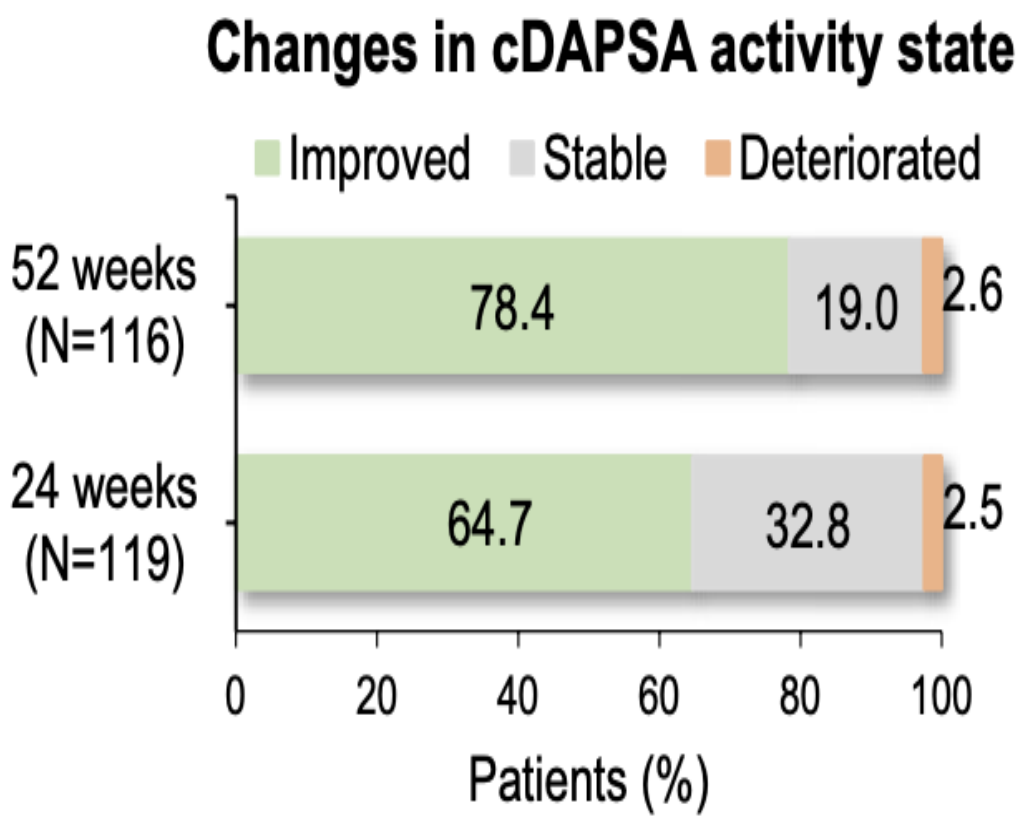


cDAPSA response in 24, and 52 weeks post-baseline

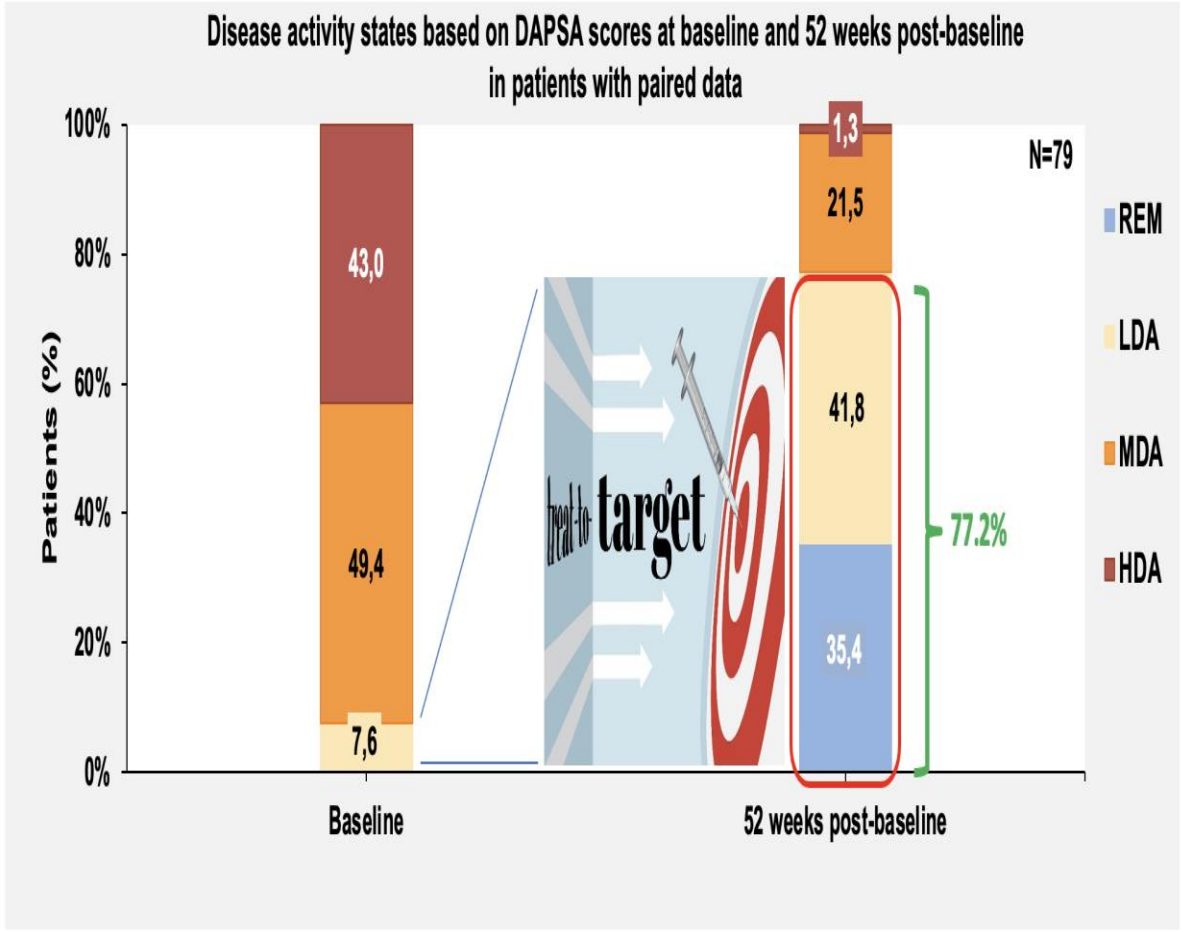
B.



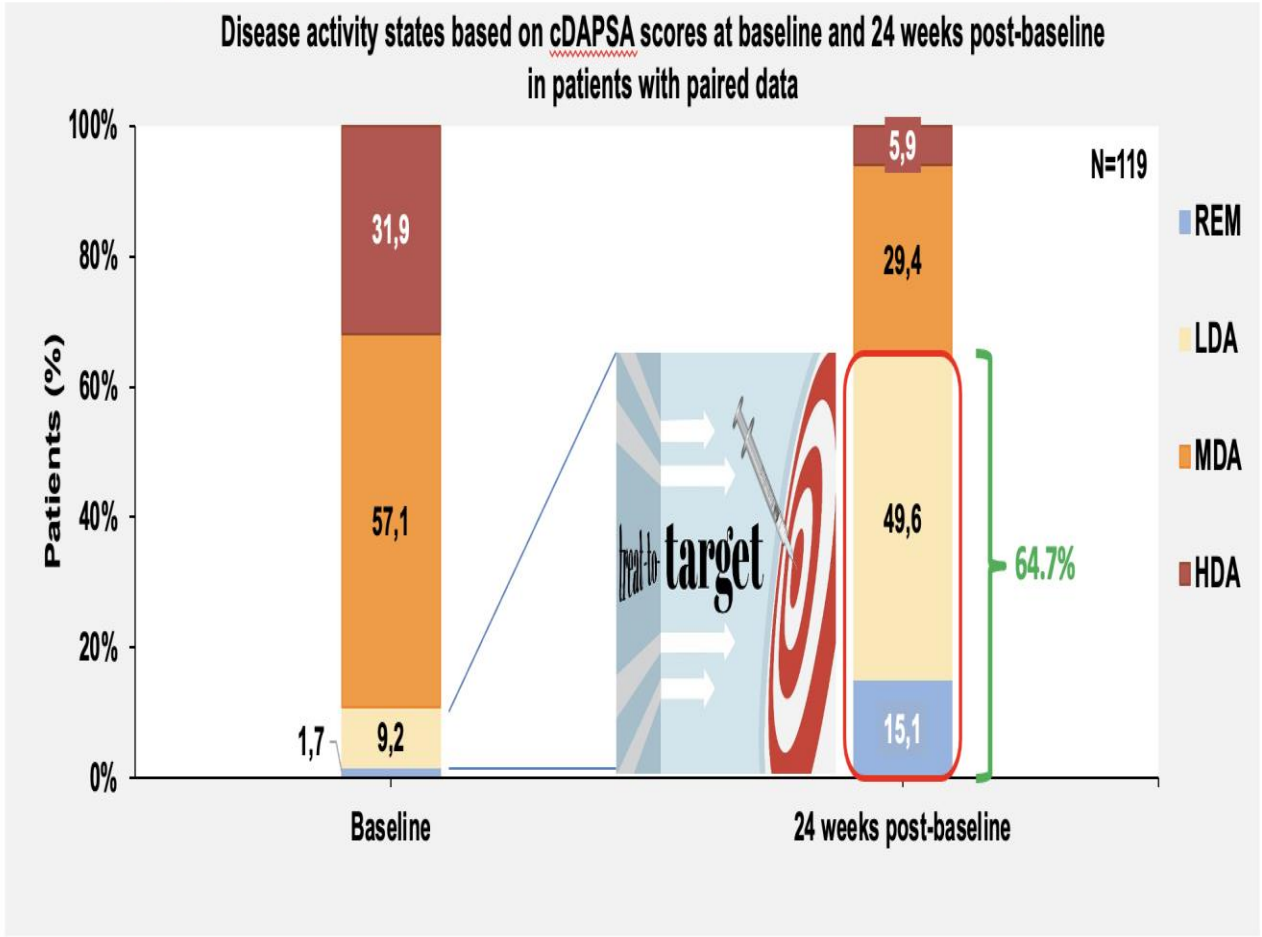
C.



DAPSA and cDAPSA activity states at baseline and 52 weeks post-baseline in patients with paired data



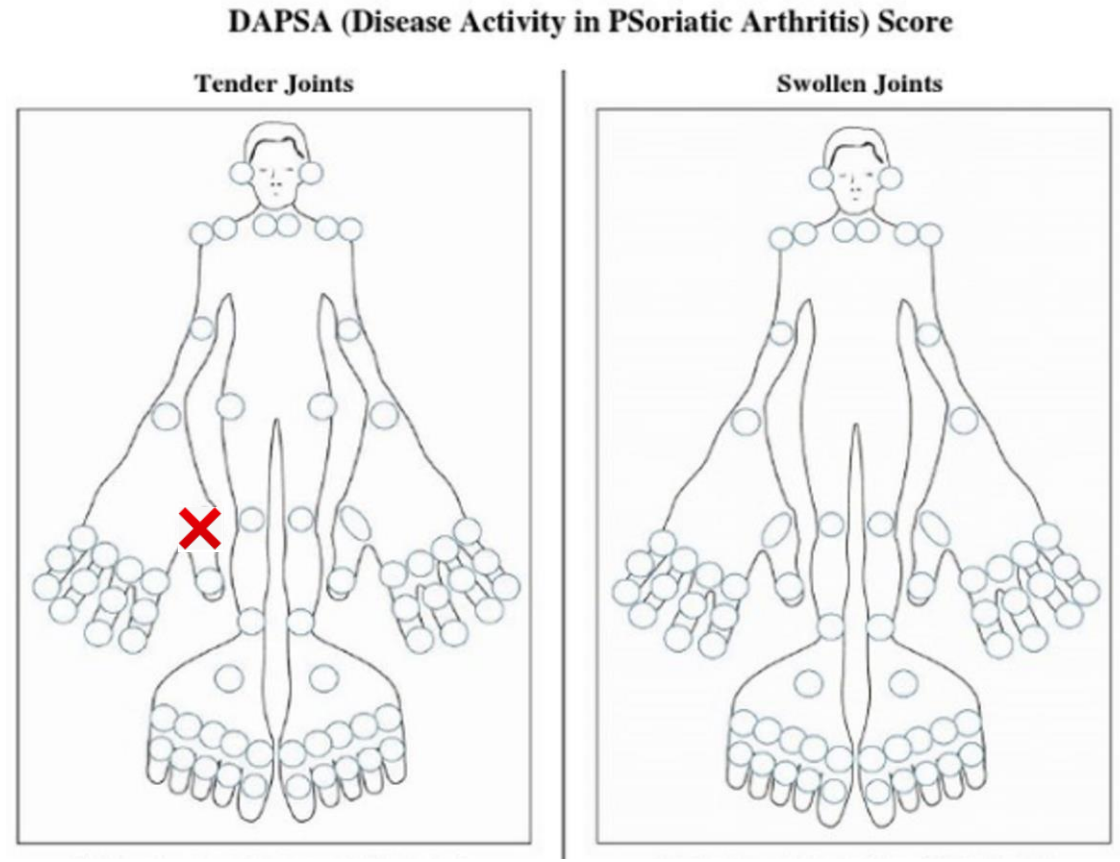
HDA, high disease activity; LDA, low disease activity; MDA, moderate disease activity; REM, remission



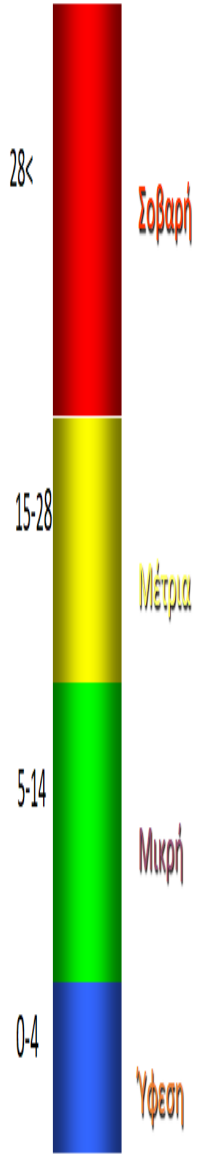
HDA, high disease activity; LDA, low disease activity, MDA, moderate disease activity; REM, remission

Case 1

- Έναρξη Appremilast 30mg 1x2 (12/2018)
- Καλή ανταπόκριση με καλή ανοχή
- Χωρίς επιδείνωση συννοσυροτήτων
- Σταθερή ηπατική λειτουργία



DAPSA: 1-3

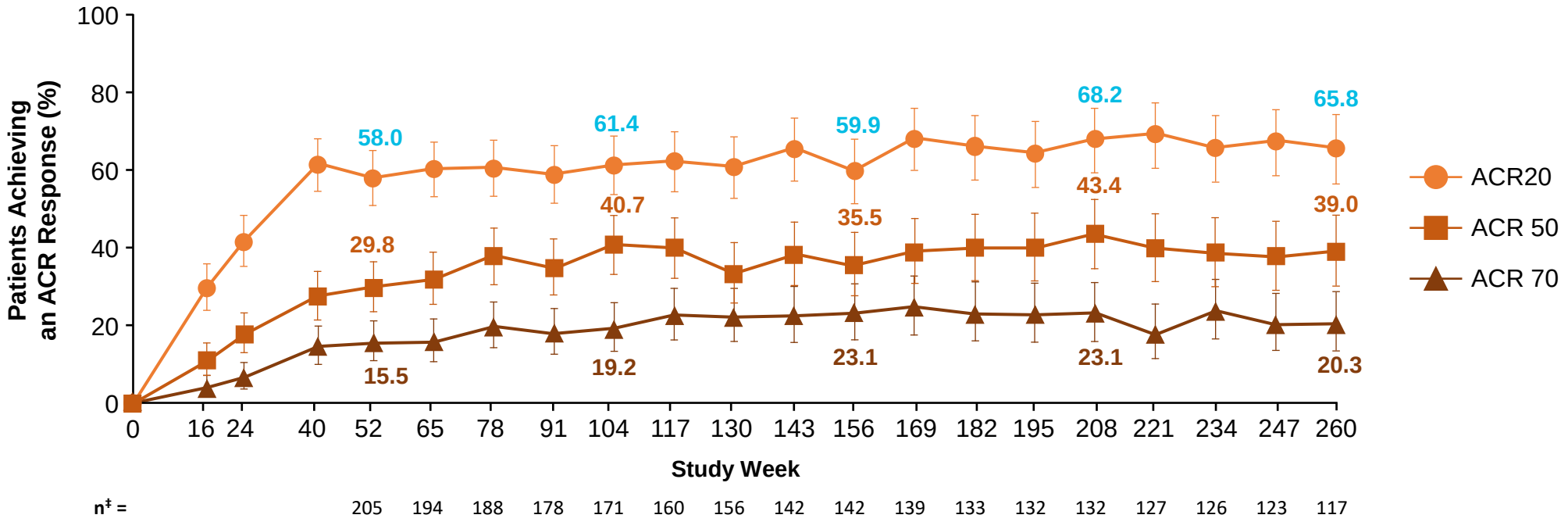


(CRP1-1.5)mg/dl? Metabolic syndrome

ACR20/50/70 Responses Were Sustained Through 5 Years With Apremilast Treatment in DMARD-naive Patients

- DMARD-naive patients with active PsA in the PALACE 4 study sustained ACR20/50/70 responses through 5 years of treatment with apremilast

ACR20/50/70 Responses Through 5 Years*,†
(Data as Observed)



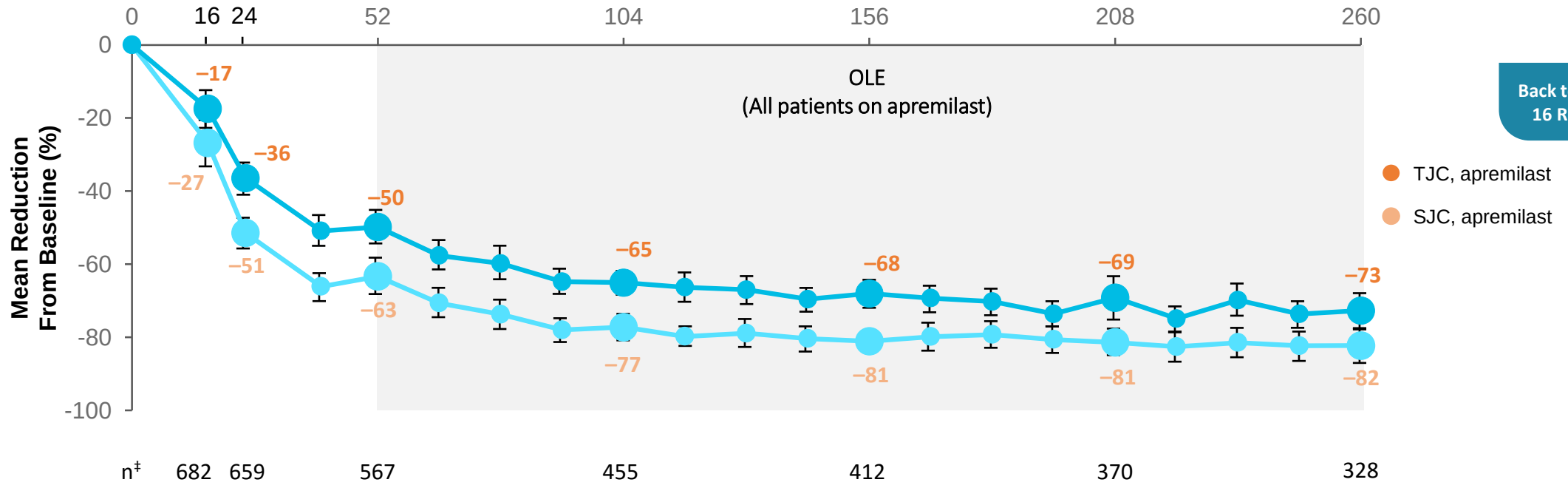
Back to Week 16 Results

*Consider OLE study limitations when interpreting results. The OLE is not blinded, is not controlled, and includes inherent self-selection bias. The OLE period was from weeks 52 to 260; †Analyses include all patient data, including the placebo-controlled period, regardless of when patients started taking apremilast (baseline, week 16, or week 24); ‡The n represents the number of patients with available data at the time point; it may vary slightly for each outcome.
ACR = American College of Rheumatology; ACR20/50/70 = ≥ 20%/50%/70% improvement in the American College of Rheumatology's core set measurements; csDMARD = conventional synthetic disease-modifying antirheumatic drug; DMARD = disease-modifying antirheumatic drug; OLE = open-label extension; PALACE = Psoriatic Arthritis Long-term Assessment of Clinical Efficacy; PsA = psoriatic arthritis.
Adapted from Wells AF, et al. *Rheumatology (Oxford)*. 2022;61:1035-1043.

Reductions in the Numbers of Swollen Joints and Tender Joints With Apremilast Were Sustained Through 5 Years

- Patients with active PsA maintained reductions in TJC and SJC with apremilast through 5 years in the pooled PALACE 1–3 studies

Mean Percent Reduction in TJC and SJC[1,2,*,†]
(Data as Observed)



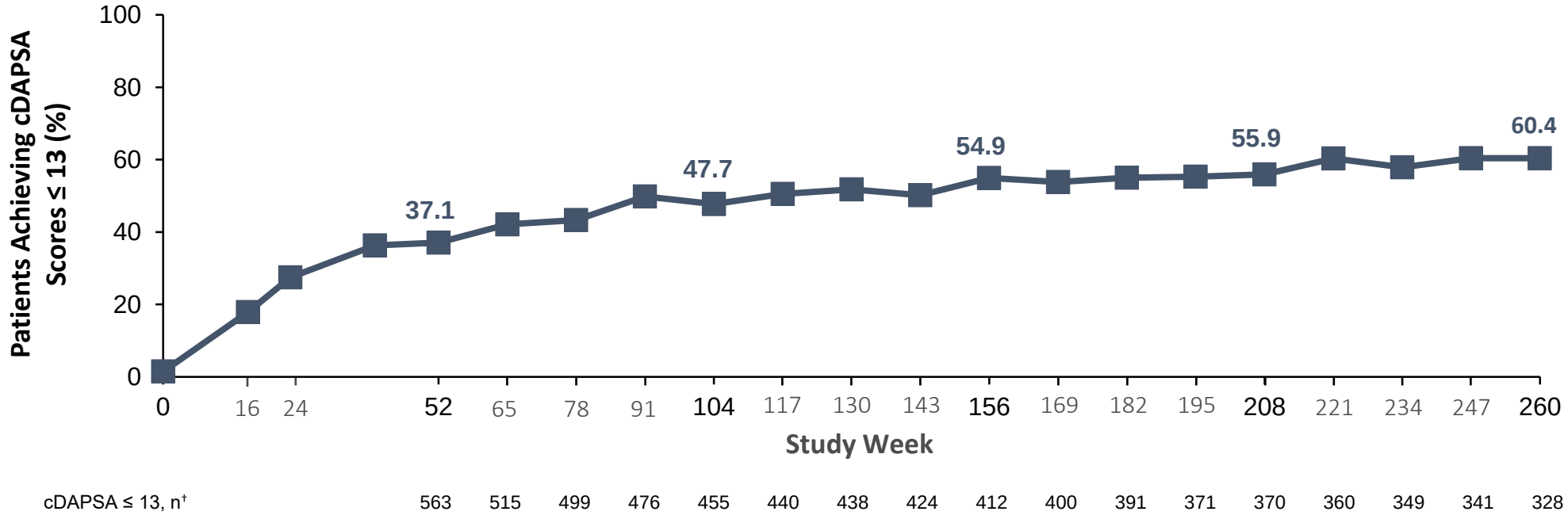
Back to Week 16 Results

*Consider OLE study limitations when interpreting results. The OLE is not blinded, is not controlled, and includes inherent self-selection bias. The OLE period was from weeks 52 to 260;[1] †Includes all patients exposed to apremilast, including during the placebo-controlled period, regardless of when patients started taking apremilast (baseline, week 16, or week 24) through week 260;[1] ‡The n at each time point represents patients with a baseline value and a postbaseline value at the time point and includes patients who discontinued early between the preceding time point and the specific time point;[2]
OLE = open-label extension; PALACE = Psoriatic Arthritis Long-term Assessment of Clinical Efficacy; PsA = psoriatic arthritis; SJC = swollen joint count; TJC = tender joint count.
1. Figure adapted with permission from Kavanaugh A, et al. *Arthritis Res Ther*. 2019;21:118; 2. Data on file, Amgen.

Two-Thirds of Patients Receiving Apremilast Achieved cDAPSA Targets by 5 Years*

- The proportion of patients achieving a cDAPSA score ≤ 13, indicative of LDA and REM, improved with longer apremilast treatment, reaching 60.4% at 5 years

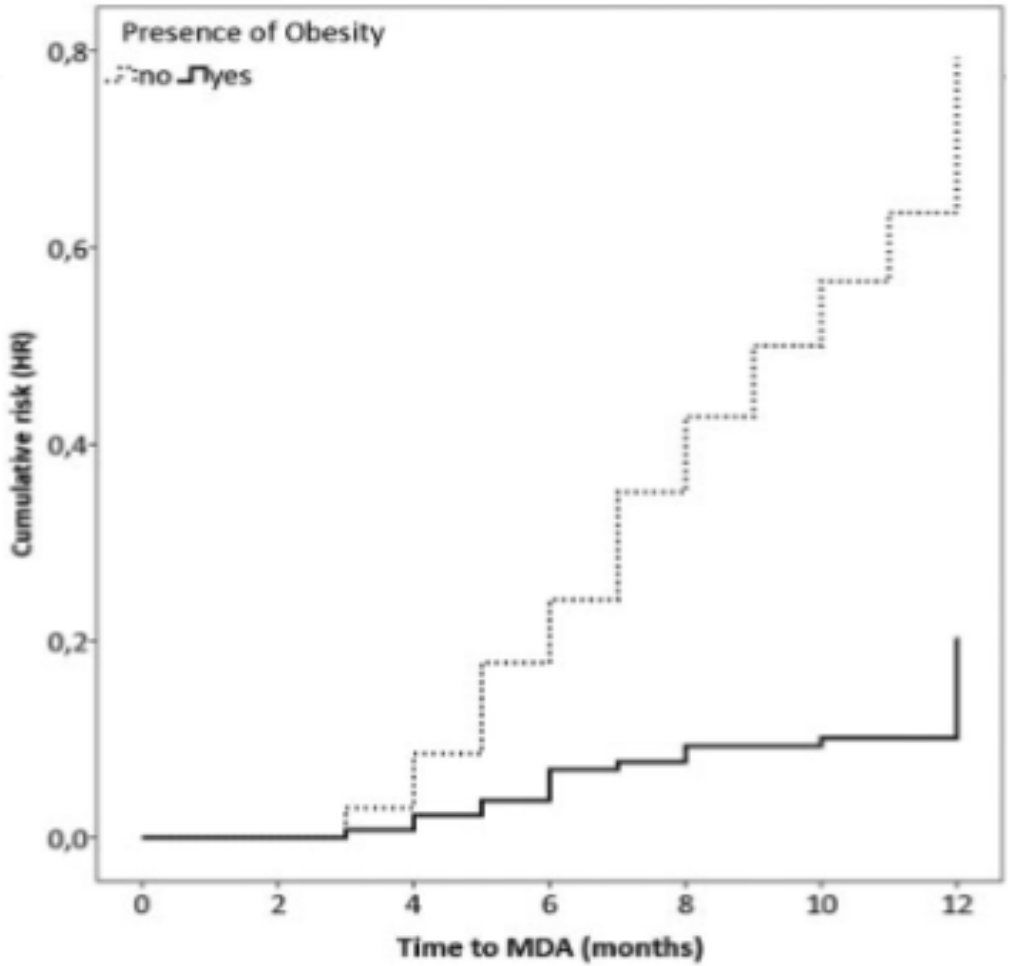
Pooled Analysis: Patients Achieving cDAPSA Scores ≤ 13*
(Data as Observed)



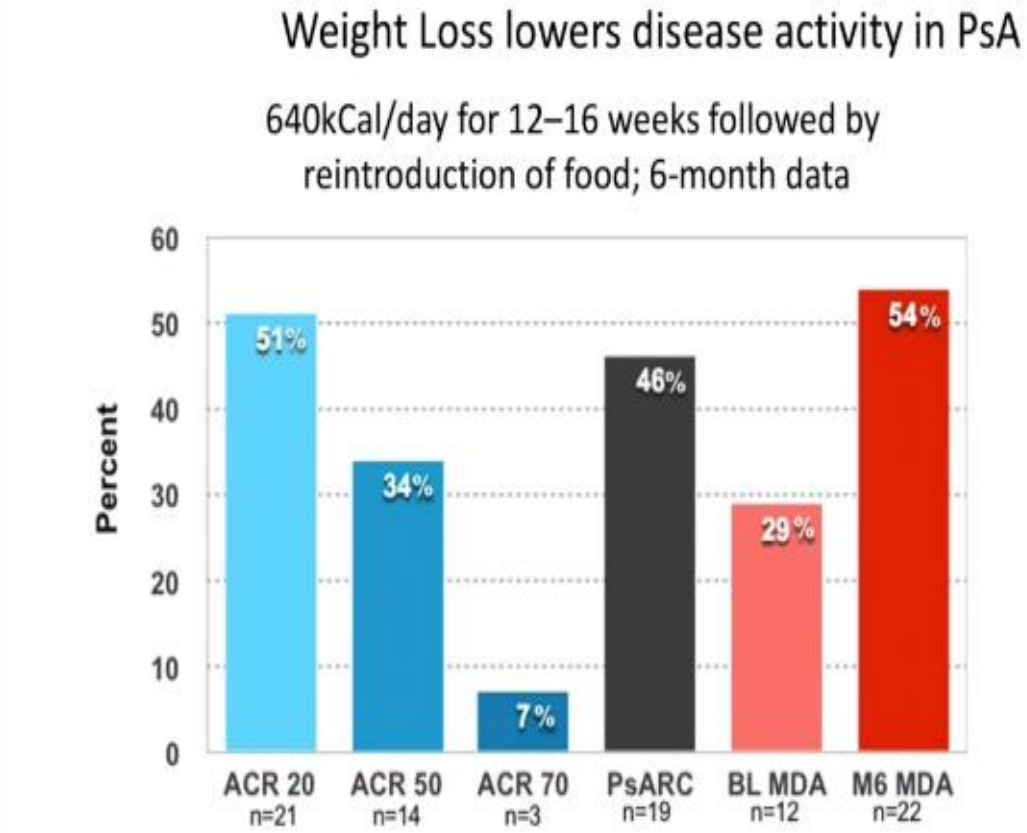
Back to Week 52 Results

*Analyses include all patient data, including the placebo-controlled period, regardless of when patients started taking apremilast (baseline, week 16, or week 24); †The n represents the number of patients with evaluable data at the time point.
cDAPSA = clinical Disease Activity Index for Psoriatic Arthritis; LDA = low disease activity; PALACE = Psoriatic Arthritis Long-term Assessment of Clinical Efficacy; PsA = psoriatic arthritis; REM = remission.
Adapted from Kavanaugh A, et al. Poster presented at: 2018 Annual Meeting American College of Rheumatology/Association of Rheumatology Health Professionals; October 19-24, 2018; Chicago, IL. Poster 686.

ΣΥΝΝΟΣΗΡΟΤΗΤΕΣ ΚΑΙ ΕΠΙΤΕΥΞΗ ΘΕΡΑΠΕΥΤΙΚΩΝ ΣΤΟΧΩΝ



Di Minno M et al, ART 2013



Klingberg E et al, ART 2019;21:17

RHEUMATOLOGY

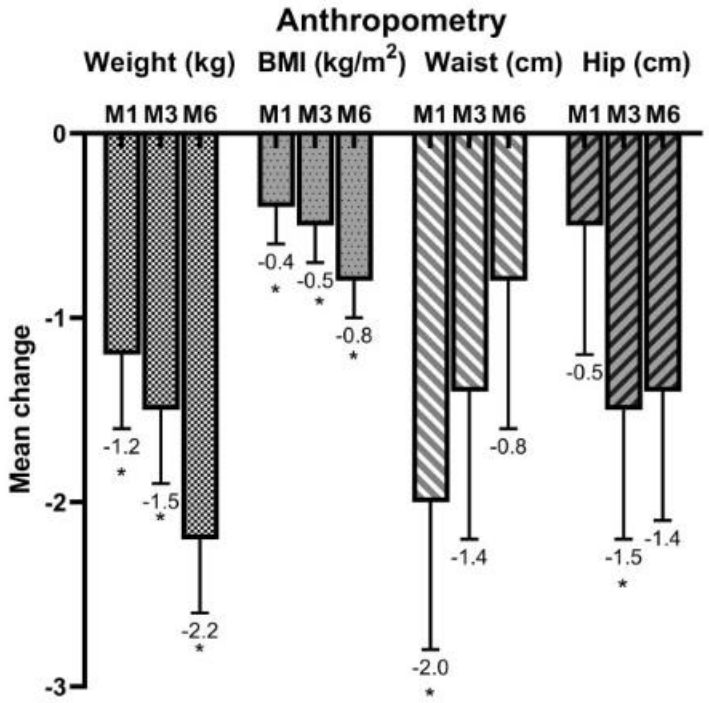
Rheumatology 2022;61:1026–1034
doi:10.1093/rheumatology/keab474
Advance Access publication 7 June 2021

Original article

Effect of the phosphodiesterase 4 inhibitor apremilast on cardiometabolic outcomes in psoriatic disease—results of the Immune Metabolic Associations in Psoriatic Arthritis study

Lyn D. Ferguson [1], Susanne Cathcart[2], Dominic Rimmer[2], Gary Semple[2], Katriona Brooksbank[1], Caron Paterson[3], Rosemary Brown[1], John Harvie[4], Xuan Gao[1], Aleksandra Radjenovic[1], Paul Welsh[1], Iain B. McInnes[3], Naveed Sattar[1] and Stefan Siebert [3]

- Apremilast treatment in 60 patients (prospective-open label)
  - mean weight loss of 2.2 kg
  - reduction in total abdominal fat [mean decrease 0.52 L (95% CI 0.08, 0.96), p=0.022]
  - principally subcutaneous adipose tissue [mean decrease 0.37 L (95% CI 0.05, 0.68), p=0.022]
  - No improvement in other metabolic parameters (no changes in glyceamic status, insulin resistance, GPL-1 activity)
  - Improved PsA disease activity
    - Irrespective of weight changes (intiinflammatory rather metabolic effects)
    - Modest nature of weight loss (??)



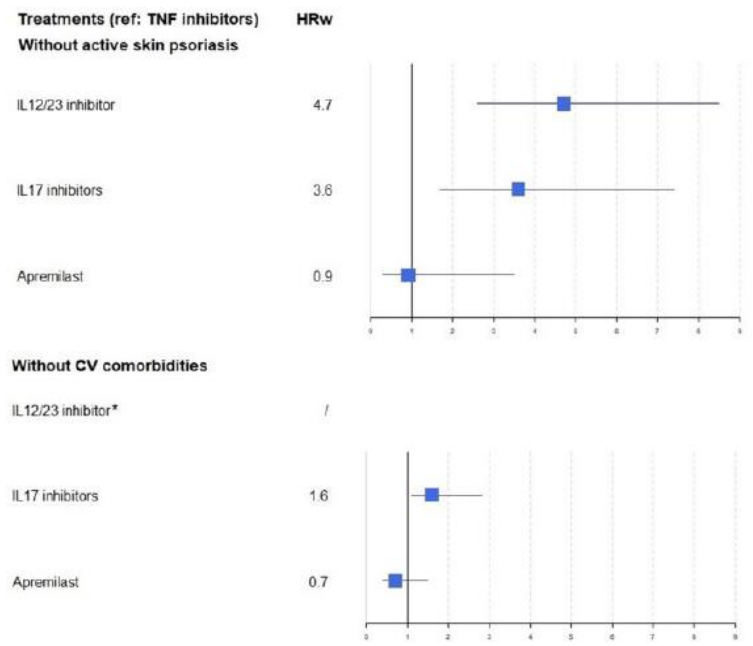
Ferguson et al. Rheumatology (Oxf) 2021

Apremilast
Reduces CVD risk

- **Patients:** PsA
- **Database:** Real-world study, French National Health Insurance (2015-9)
- 9510 bDMARD and 1885 apremilast **new users**, without CVD history
- **Primary endpoint**: occurrence of MACEs
- Vs TNFi
  - **Apremilast: Equal**
  - **IL-12/23: (HR) 2.0, (95% CI 1.3, 3.0)**
  - **IL-17 inhibitors: HR: 1.9, (95% CI 1.2, 3.0)**
  - In a sub-analysis in patients without CV risk factors,
    - MACEs occurred more frequently with IL-17 inhibitors than with TNFi (HRw 1.6, 95% CI 1.1, 2.8)

  - However…..possible biases (e.g skin involvement and IL-17i)

FIG. 2 Forest plot of risk of major adverse cardiac events by therapeutic drug class in subgroup analyses



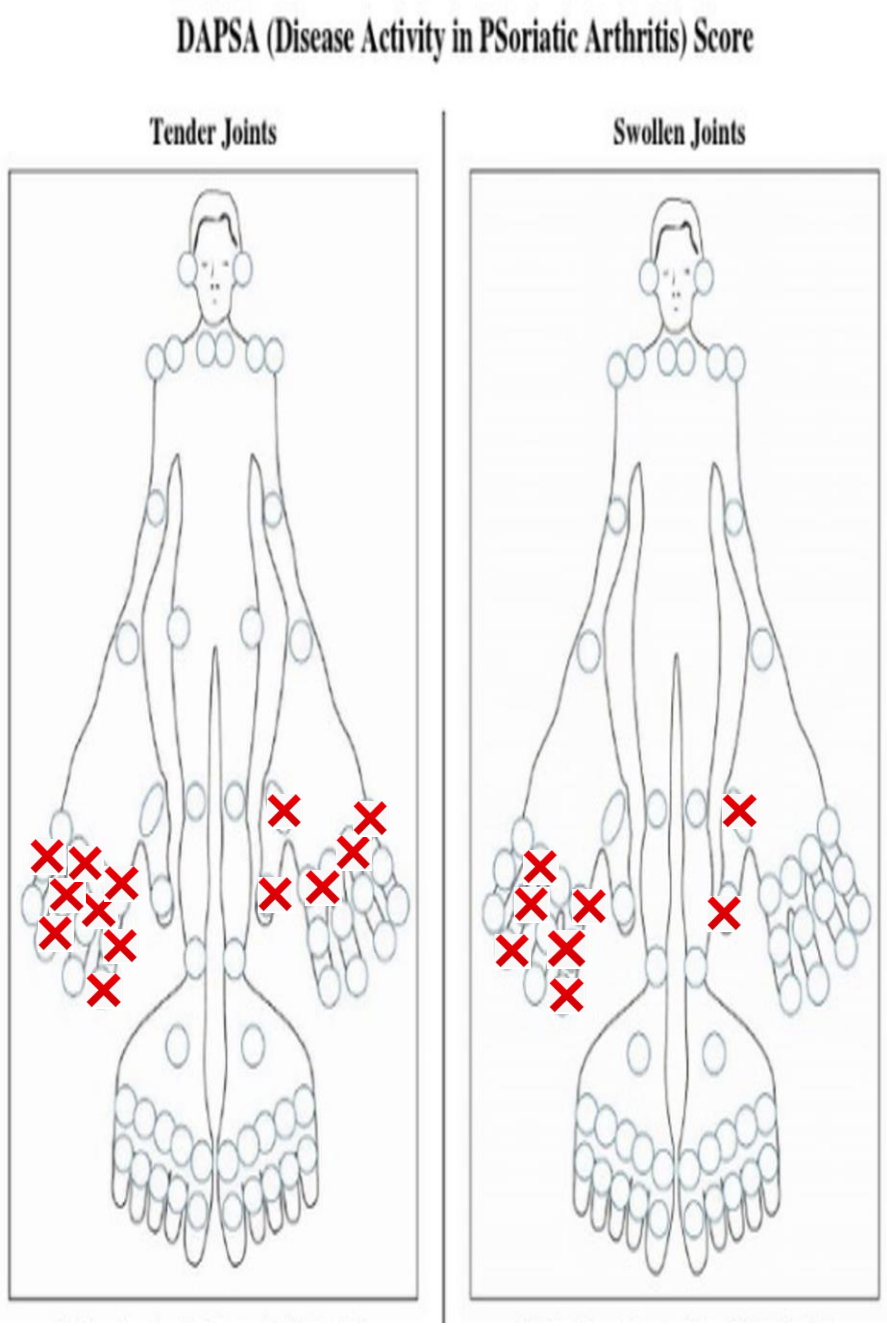
*Not available due to the absence of events in this class. HR_w: weighted hazard ratio; CV: cardiovascular.

Pina Vegas Rheumatology (Oxf) 2021
Gialouri et al Rheumatology (Oxf) 2021

Case 2

- Άνδρας 48 ετών (επιχειρηματίας) – 4/2020
- Αρθραλγίες μικρών αρθρώσεων των χεριών
- Δακτυλίτιδα μεγάλου δακτύλου (ΑΡ), δείκτη και παράμεσου (ΔΕ)
- Ατομικό ιστορικό: χωρίς κάτι ιδιαίτερο
- Χωρίς ιστορικό δερματικής ψωρίασης
- Αδελφός: ψωρίαση δέρματος

Case 2



- How active was your rheumatic disease on average during the last week?

not active 0 1 2 3 X 5 6 7 8 9 10 very active

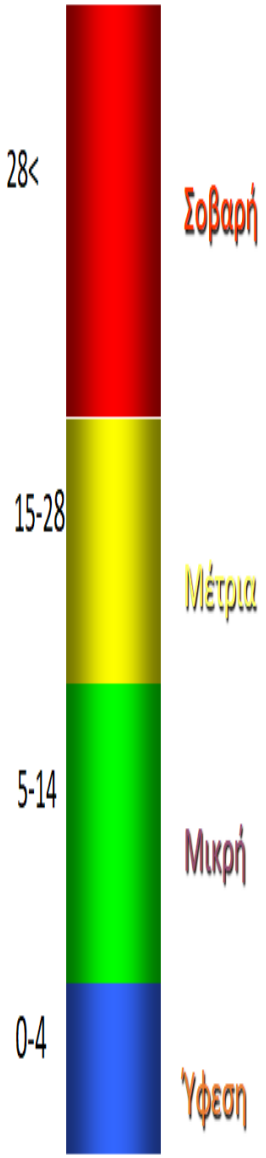
- How would you describe the overall level of joint pain during the last week?

none 0 1 2 3 X 5 6 7 8 9 10 very severe

Πρωϊνή δυσκαμψία > 30 min
HLA B27 (-)
Δακτυλίτιδα
BSA:0

DAPSA: 40
Επώδυνες: 21
Διογκωμένες:8
CRP: 0,71 (.5)mg/dl

DMARD naïve
Πολυαρθριτικός τύπος
Δακτυλίτιδα



Case 2

- Συζήτηση για MTX - επιφυλακτικός
- Έναρξη 15 mg/week
- Ναυτία – Διακοπή

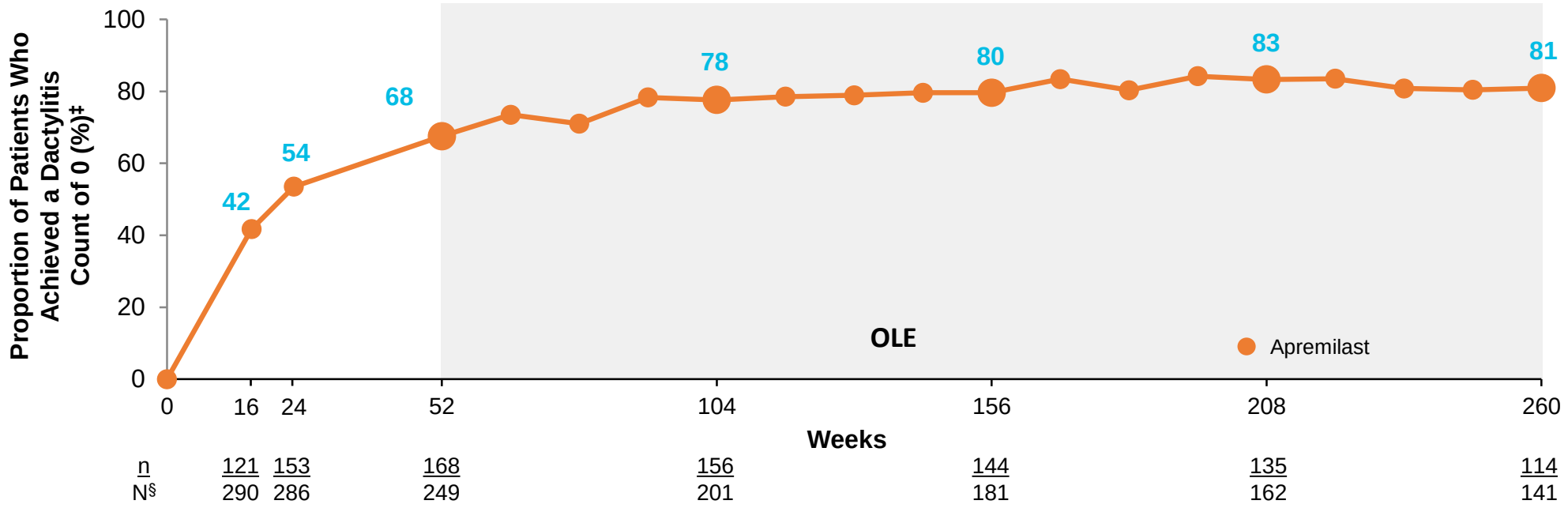
- Life style ασθενή (επιθυμίες ασθενή)
- Αγωγή από του στόματος
- Χωρίς τακτικούς αιματολογικούς ελέγχους

- Έναρξη Appremilast

Resolution of Dactylitis Was Sustained Through 5 Years With Apremilast Treatment

- Patients with preexisting dactylitis at baseline maintained resolution of dactylitis with apremilast through 5 years in the pooled PALACE 1–3 studies

Proportion of Patients Achieving Dactylitis Count of 0 Through 5 Years[1,2,*,†]
(Data as Observed)



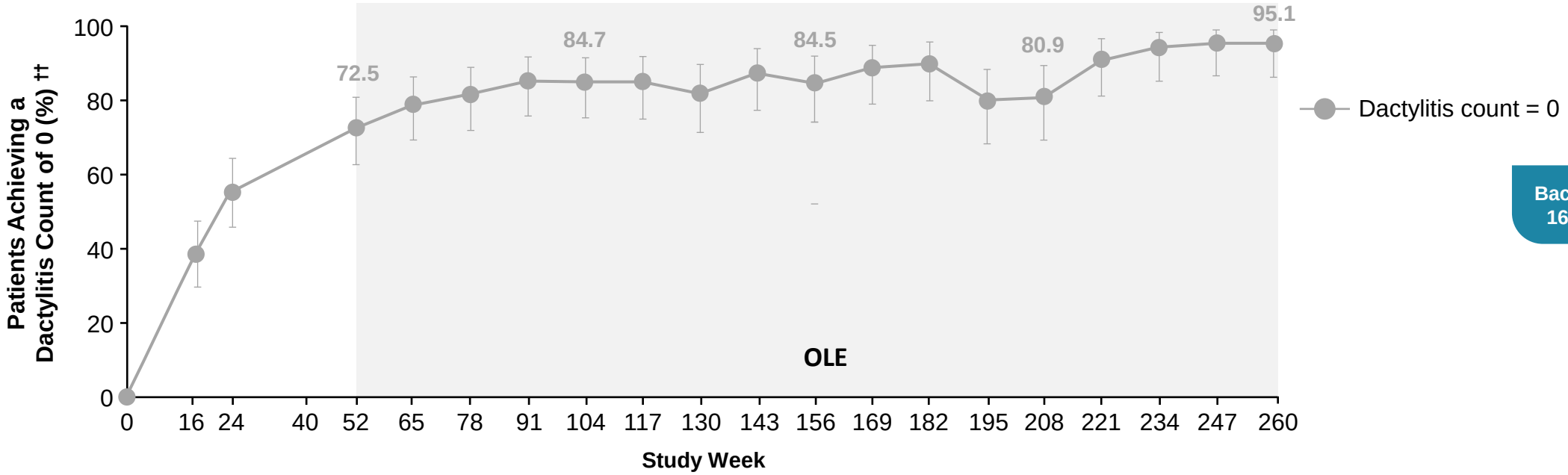
Back to Week 24 Results

*Consider OLE study limitations when interpreting results. The OLE is not blinded, is not controlled, and includes inherent self-selection bias. The OLE period was from weeks 52 to 260;[1] †Includes all patients exposed to apremilast, including during the placebo-controlled period, regardless of when patients started taking apremilast (baseline, week 16, or week 24) through week 260;[1] ‡Dactylitis severity count = 0–20; a score of 0 indicates resolution of dactylitis;[2] §n/N, number of responders/number of patients who had sufficient data for a definitive determination of response status at the time point, which includes patients who discontinued early between the preceding time point and the specific time point.[1]
OLE = open-label extension; PALACE = Psoriatic Arthritis Long-term Assessment of Clinical Efficacy; PsA = psoriatic arthritis.
1. Figure adapted with permission from Kavanaugh A, et al. *Arthritis Res Ther*. 2019;21:118; 2. Data on file, Amgen.

Resolution of Dactylitis Was Sustained Through 5 Years in DMARD-naive Patients Treated With Apremilast

- csDMARD- and biologic-naive patients with preexisting dactylitis at baseline maintained resolution of dactylitis with apremilast through 5 years in the PALACE 4 study

Proportion of Patients Achieving Dactylitis Count of 0 Through 5 Years[1,2,*,†,‡,§,**]
(Data as Observed)



Dactylitis count = 0, n	102	99	92	87	85	79	77	71	71	71	68	69	68	66	66	64	61

Back to Week 16 Results

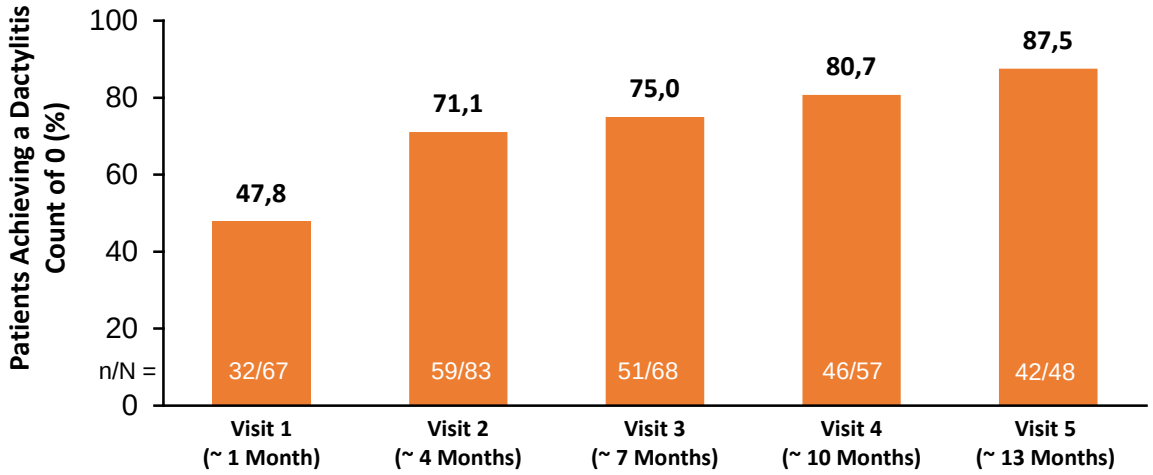
*Examined among patients with dactylitis at baseline (n = 129); †Includes all patients exposed to apremilast, including during the placebo-controlled period, regardless of when patients started taking apremilast (baseline, week 16, or week 24) through week 260; ‡Data are presented "as observed" with no imputation for missing values in order to describe outcomes among those patients who continued to receive treatment over 260 weeks; §The OLE period was from weeks 52 to 260; **Patients discontinued treatment during the study because of AEs, lack of efficacy, and other (withdrawal by patient, loss of follow-up, protocol violation, nonadherence, and other); †† Dactylitis severity score = 0–20; a score of 0 indicates resolution of dactylitis.
AE = adverse event; csDMARD = conventional synthetic disease-modifying antirheumatic drug; DMARD = disease-modifying antirheumatic drug; OLE = open-label extension; PALACE = Psoriatic Arthritis Long-term Assessment of Clinical Efficacy; PsA = psoriatic arthritis.
1. Data on file, Amgen; 2. Adapted from Wells AF, et al. Rheumatology (Oxford). 2022;61:1035-1043.

Improvement in **Dactylitis and Enthesitis** Observed 1 Month After Apremilast Initiation and Through 13 Months

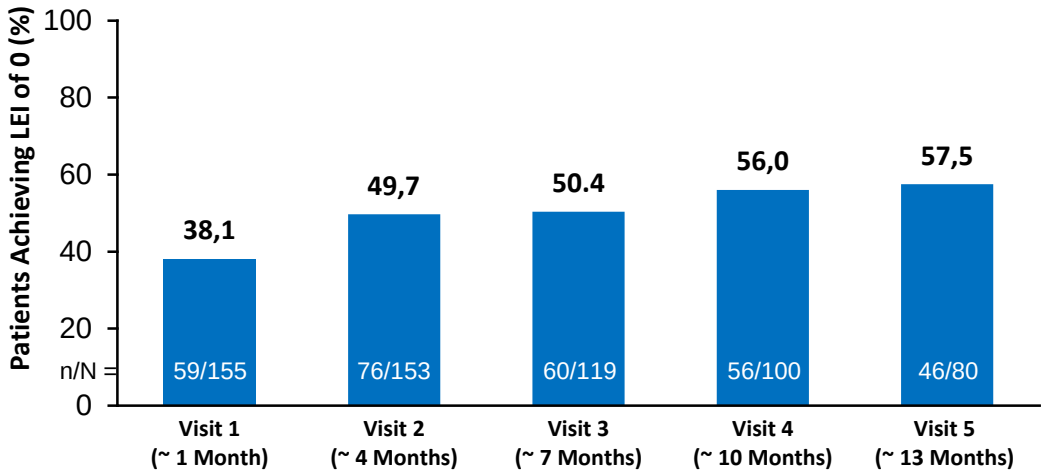
- In LAPIS-PsA, resolution of dactylitis and enthesitis were observed as early as 1 month and sustained for up to 13 months with apremilast treatment

Baseline Characteristics	
Dactylitis,* n/N (%)	96/418 (23.0)
Dactylitis count,† mean (SD)	2.2 (2.0)
Enthesitis (LEI),* n/N (%)	195/418 (46.7)
LEI (0-6), ‡ mean (SD)	2.9 (1.7)

Patients Achieving Dactylitis Count of 0†



Patients Achieving LEI of 0‡



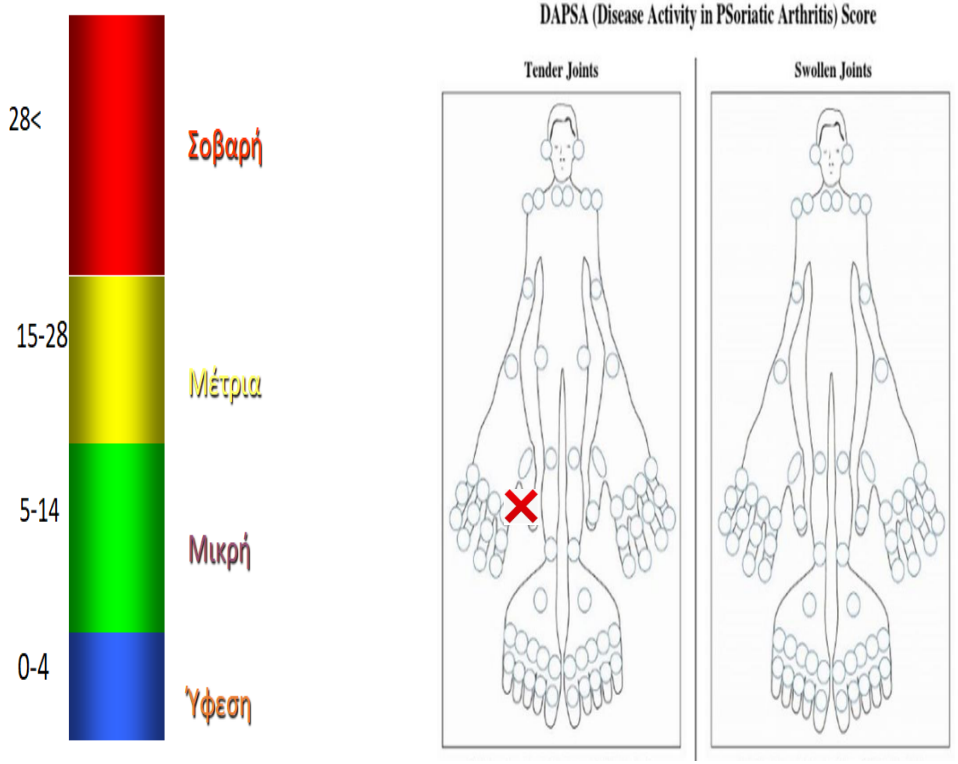
*Number of patients with enthesitis, dactylitis, or nail involvement among patients with data available at baseline; †In patients with dactylitis at baseline; ‡In patients with enthesitis at baseline.
LAPIS-PsA = Long-term Documentation on the Use of Apremilast in Patients With Psoriatic Arthritis in Practice Conditions; LEI = Leeds Enthesitis Index; PsA = psoriatic arthritis; SD = standard deviation.
Wollenhaupt J, et al. Poster presented at: 2020 European E-Congress of Rheumatology; June 3-6, 2020. Poster FRI0365.

Case 2

- Συζήτηση για MTX - επιφυλακτικός
- Έναρξη 15 mg/week
- Ναυτία – Διακοπή

- Life style ασθενή
  - Αγωγή από του στόματος
  - Χωρίς τακτικούς αιματολογικούς ελέγχους

- Έναρξη Appremilast (5/2020)



- How active was your rheumatic disease on average during the last week?

not active 1 2 3 4 5 6 7 8 9 10 very active

- How would you describe the overall level of joint pain during the last week?

none 1 2 3 4 5 6 7 8 9 10 very severe

DAPSA: 0-1

Apremilast Has a **Consistent Safety Profile** Across Multiple Clinical Trials and Disease States

		Placebo (%) n = 506	Apremilast (%) n = 920
PsO[1]	**ARs Reported in ≥ 5% of Patients Taking Apremilast**		
	Diarrhea	6	17
	Nausea	7	17
	URTI	6	9
	Tension headache	4	8
	Headache	4	6
PsA[1,*]	**ARs Reported in ≥ 2% of Patients Taking Apremilast and ≥ 1% Higher Than That Observed in Patients on Placebo***		
		n = 490	n = 493
	Diarrhea	1.6	7.7
	Nausea	3.1	8.9
	Headache	2.2	5.9
	URTI	1.8	3.9
	Vomiting	0.4	3.2
	Nasopharyngitis	1.6	2.6
	Upper abdominal pain	0.2	2.0

*For up to 16 weeks (after the initial 5-day titration); †For up to 12 weeks.
ARs = adverse reactions; BD = Behçet's disease; PsA = psoriatic arthritis; PsO = psoriasis; URTI = upper respiratory tract infection.
1. Data on file, Amgen; 2. Hatemi G, et al. *N Engl J Med*. 2019;381:1918-1928.

The Incidence Rates of the Most Common AEs Did Not Increase With Increased Exposure to Apremilast Through 5 Years

During the apremilast-exposure period, **most cases of diarrhea and nausea were mild or moderate** in severity, occurred during the first 2 weeks of apremilast exposure, and **generally resolved** in 1 month; low rates of discontinuation of apremilast because of diarrhea (1.5%) and nausea (1.7%) were observed

Most Commonly Reported AEs in the Pooled Population

	Placebo-Controlled Period* Weeks 0–16 or 24				Apremilast-Exposure Period† Weeks 0 to ≥ 260	
	Placebo (n = 1,089) 344.3 pt-yrs		Apremilast (n = 1,504) 520.1 pt-yrs		Apremilast (n = 2,157) 5,163.1 pt-yrs	
Most Common ARs (≥ 5%)‡	n (%)	EAIR 100 pt-yrs	n (%)	EAIR/ 100 pt-yrs	n (%)	EAIR/ 100 pt-yrs
Nausea	56 (5.1)	16.8	246 (16.4)	54.4	361 (16.7)	8.1
Diarrhea	45 (4.1)	13.5	234 (15.6)	51.7	372 (17.2)	8.4
Headache	41 (3.8)	12.2	119 (7.9)	24.4	218 (10.1)	4.6
URTI	46 (4.2)	13.6	107 (7.1)	21.3	376 (17.4)	8.5
Nasopharyngitis	47 (4.3)	13.9	85 (5.7)	16.8	320 (14.8)	7.1

*Patients as initially randomized at week 0 who received ≥ 1 dose of study medication during the placebo-controlled period (0 to 16 or 24 weeks); †The apremilast-exposure period (0 to ≥ 260 weeks) includes all patients who received apremilast regardless of when apremilast exposure started (week 0, week 16, or week 24). Apremilast exposure is based on each patient's total exposure to apremilast, defined as the time interval between the dates of the first and last doses of apremilast, through December 2017; ‡ARs occurring in ≥ 5% of patients in any treatment group during the placebo-controlled period.

AEs = adverse events; ARs = adverse reactions; EAIR = exposure-adjusted incidence rate; ESTEEM = Efficacy and Safety Trial Evaluating the Effects of Apremilast in Psoriasis; PALACE = Psoriatic Arthritis Long-term Assessment of Clinical Efficacy; PsA = psoriatic arthritis; PsO = psoriasis; pt-yrs = patient-years; URTI = upper respiratory tract infection.

Callis-Duffin K, et al. Poster presented at: American Academy of Dermatology Virtual Meeting Experience 2020; June 12–14, 2020. Poster 15114.

The Incidence Rates of AEs of Special Interest Remained Low Through 5 Years of Apremilast Exposure*

Additional MACE 5-Year Data

Incidence of MACE, Malignancies, and Serious Infections in 6 Phase 3 Trials[1,2]

	Placebo-Controlled Period Weeks 0–16 or 24				Apremilast-Exposure Period Weeks 0 to ≥ 260	
	Placebo N = 1,089* 344.3pt-yrs		Apremilast N = 1,504* 520.1pt-yrs		Apremilast N = 2,157 5,163.1 pt-yrs	
	n (%)	EAIR/ 100 pt-yrs	n (%)	EAIR/ 100 pt-yrs	n (%)	EAIR/ 100 pt-yrs
MACE and Potential MACE†	24 (2.2)	7.0	36 (2.4)	7.0	193 (8.9)	4.0
Malignancy	5 (0.5)	1.5	7 (0.5)	1.3	51 (2.4)	1.0
Opportunistic Infection	13 (1.2)	3.8	7 (0.5)	1.3	76 (3.5)	1.5
Latent TB	0 (0.0)	0.0	0 (0.0)	0.0	1 (< 0.1)	0.0

During the apremilast-exposure period, 1 patient treated with apremilast had an adverse reaction of latent TB (chest x-ray was negative). The patient was treated with isoniazid.[2]

*Pooled data from 6 Phase 3 studies: ESTEEM 1 and 2 and PALACE 1-4;[2] †MACE was defined as TEAEs of sudden unwitnessed death, cardiovascular death (sudden cardiac death, death due to myocardial infarction, death due to heart failure, death due to stroke, and death due to other cardiovascular causes), myocardial infarction, and nonfatal stroke. Potential MACE was defined as unstable angina requiring hospitalization, coronary revascularization procedure, transient ischemic attack, re-hospitalization for recurrent ischemia, embolic events, and deep vein thrombosis.[1]

EAIR = exposure-adjusted incidence rate; ESTEEM = Efficacy and Safety Trial Evaluating the Effects of Apremilast in Psoriasis; MACE = major adverse cardiovascular events; PALACE = Psoriatic Arthritis Long-term Assessment of Clinical Efficacy; PsA = psoriatic arthritis; PsO = psoriasis; pt-yrs = patient-years; TB = tuberculosis; TEAEs = treatment-emergent adverse events.

1. Data on file, Amgen; 2. Callis-Duffin, et al. Poster presented at: American Academy of Dermatology Virtual Meeting Experience 2020; June 12-14, 2020. Poster 15144.

Tuberculosis and targeted synthetic or biologic DMARDs, beyond tumor necrosis factor inhibitors

Gerasimos Evangelatos, Vasiliki Koulouri, Alexios Iliopoulos and George E Fragoulis

Table 4. Cases of tuberculosis (TB) and relative incidence rate (IR) in patients receiving IL-12, IL-23, IL-17 inhibitors.

IL-12, IL-23, IL-17 Inhibitors								
Drug	**Disease**	**Study type**	**No~**	**Pt-yrs**	**Active TB cases**	**IR§**	**Rate general population***	**Reference**
Ustekinumab	PsA, PsO, CD	RCT	5884	4521	1	22.12	International	Ghosh *et al.*[76]
Ustekinumab	PsA	RCT	705	NA	0	NA	International	Ritchlin *et al.*[72]
Ustekinumab	PsA	LTE	615	NA	0	NA	International	Kavanaugh *et al.*[73]
Ustekinumab	PsA	RLS	65	NA	0	NA	7.0 (Italy)	Chimenti *et al.*[74]
Ustekinumab	CD	RCT	1177	NA	1	NA	International	Feagan *et al.*[75]
Ustekinumab	PsO	LTE	3117	8998	0	0.0	International	Lopez-Ferrer *et al.*[77]
Guselkumab	PsA	Phase II	100	NA	0	NA	International	Deodhar *et al.*[85]
Guselkumab	RA	Phase II	110	NA	0	NA	International	Smolen *et al.*[86]
Guselkumab	PsO	RCT	1283	NA	0	NA	International	Crowley *et al.*[87]
Rizankizumab	PsA	RCT	185	NA	0	NA	International	Mease *et al.*[88]
Rizankizumab	PsO	RCT	588	NA	0	NA	International	Crowley *et al.*[87]
Rizankizumab	PsO	RCT	301	NA	0	NA	International	Reich *et al.*[89]
Secukinumab	AS, PsA, PsO	RCT	7355	16,227	0	NA	International	Deodhar *et al.*[95]
Secukinumab	AS, PsA, PsO	LTE	NA	96,054	1	5.0	International	Deodhar *et al.*[95]
Secukinumab	PsO	RCT	3430	2725	0	0.0	International	van de Kerkhof *et al.*[96]
Secukinumab	PsO	RLS	96	104.5	0	0.0	43.0 (Taiwan)	Wu *et al.*[83]

Targeted synthetic DMARDs								
Drug	**Disease**	**Study type**	**No~**	**Pt-yrs**	**Active TB cases**	**IR§**	**Rate general population***	**Reference**
Apremilast	PsO	RCT, LTE	1184	3671.3	0	0.0	International	Crowley *et al.*[39]
Apremilast	PsA	RCT	1644	NA	0	0.0	International	Cutolo *et al.*[35]; Edwards *et al.*[36]; Kavanaugh *et al.*[37]; Wells *et al.*[38]
Apremilast	PsA	RLS	202	101.0	0	0.0	7.0 (Italy)	Abignano *et al.*[40]; Favalli *et al.*[41]
Tofacitinib	RA	RCT, LTE	5671	12,664.0	26	210.0	International	Winthrop *et al.*[47]
Tofacitinib	RA	RCT, LTE	6194	19,406.0	36	200.0	International	Cohen, *et al.*[49]
Tofacitinib	PsA	RCT	394	NA	0	0.0	International	Gladman *et al.*[50]
Tofacitinib	PsA	RCT	316	NA	0	0.0	International	Mease *et al.*[51]
Tofacitinib	UC	RCT	1157	1612.8	0	0.0	International	Sandborn *et al.*[54]
Baricitinib	RA	RCT, LTE	3492	6636.7	10	150.0	International	Smolen *et al.*[56]
Baricitinib	RA	RCT, LTE	740	1294	3	230.0	East Asia	Chen *et al.*[57]
Baricitinib	RA	RCT, LTE	540	851.5	0	0.0	14.0 (Japan)	Harigai *et al.*[58]
Baricitinib	RA	LTE	201	433.9	0	0.0	International	Keystone *et al.*[59]
Upatacitinib	RA	RCT	2022	NA	1	NA	International	Burmester *et al.*[60]; Fleischmann *et al.*[61]; Genovese *et al.*[62]; Smolen *et al.*[63]
Filgotinib	RA	RCT	1128	NA	0	0.0	International	Genovese *et al.*[65]; Kavanaugh *et al.*[66]; Westhovens *et al.*[68]

Evangelatos G, Ther Adv Musculoskelet Dis. 2020 Jun 22;12:1759720X20930116

Clinical Study

The Pharmacodynamic Impact of Apremilast, an Oral Phosphodiesterase 4 Inhibitor, on Circulating Levels of Inflammatory Biomarkers in Patients with Psoriatic Arthritis: Substudy Results from a Phase III, Randomized, Placebo-Controlled Trial (PALACE 1)

Peter H. Schafer,[1] Peng Chen,[2] Lorraine Fang,[2] Andrew Wang,[2] and Rajesh Chopra[1]

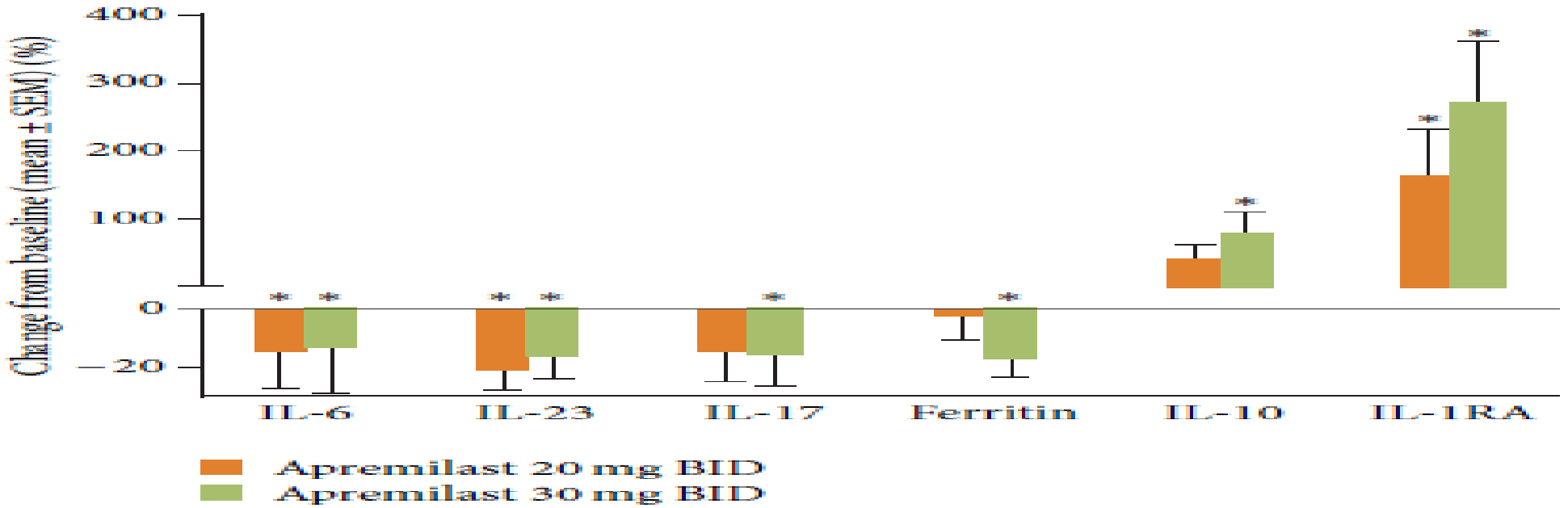


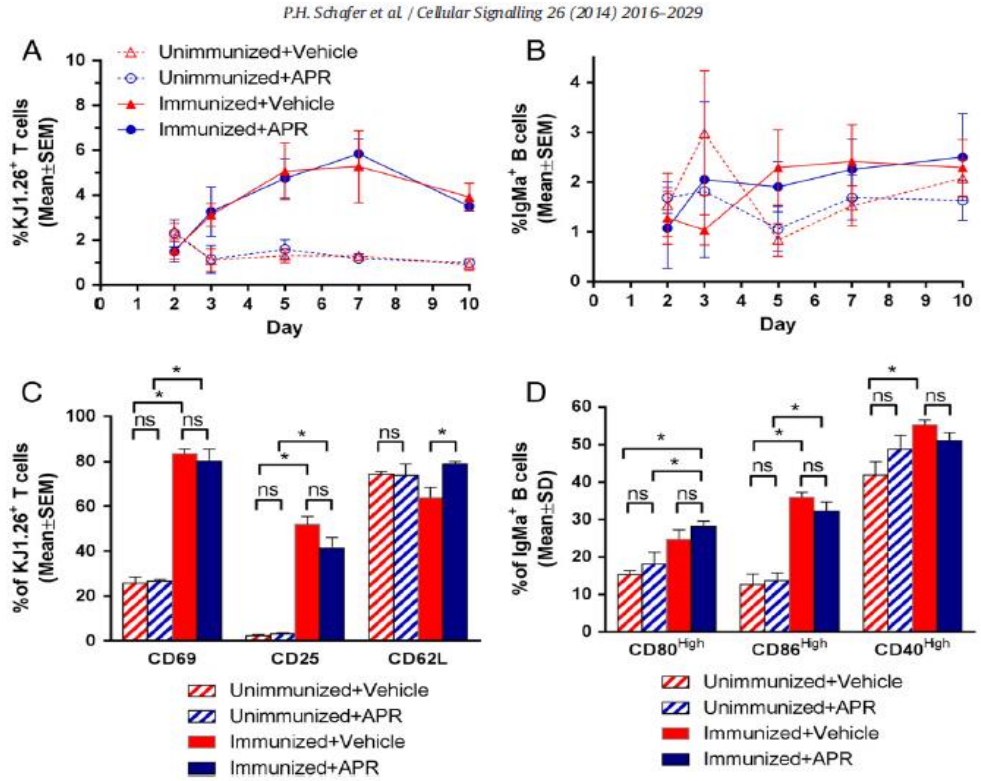
FIGURE 3: Mean percent change in biomarkers with apremilast 20 mg BID and apremilast 30 mg BID at Week 40; no patients were receiving placebo at this time point. $^{*}P < 0.05$ Wilcoxon signed rank test (two-sided P value for testing the median of zero).

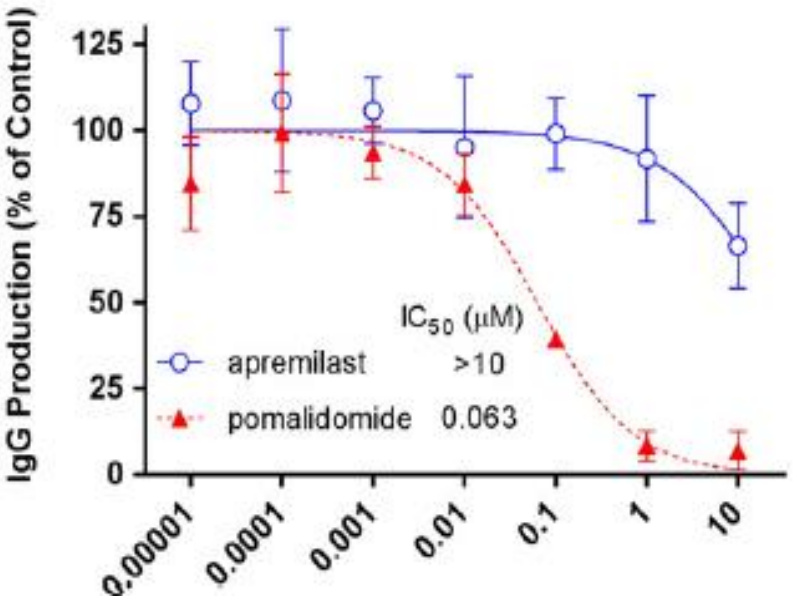
Journal of Immunology Research Volume 2015, Article ID906349

Cellular Signalling

Apremilast is a selective PDE4 inhibitor with regulatory effects on innate immunity

P.H. Schafer et al. / Cellular Signalling 26 (2014) 2016–2029





✓APPREMILAST DOES NOT AFFECT THE CLONAL EXPANSION OF T- AND B-CELLS AND ANTIBOBY RESPONSE IN VITRO

✓NO REDUCTION IN INTERFERON-γ

Take home message

Το apremilast

✓ αποτελεί αξιόπιστη θεραπευτική επιλογή σε ασθενείς με ψωριασική αρθρίτιδα με πολύ καλή ανταπόκρισηπου φτάνει και ξεπερνάει τα 5 έτη είτε σε κλινικές μελέτες είτε σε RWD

✓ μπορεί να χορηγηθεί σε ασθενείς που δεν έχουν λάβει βιολογικά ή συνθετικά τροποποιητικά με πολύ καλά αποτελέσματα

✓ παρουσιάζει πολύ θετικά αποτελέσματα σε ειδικές κλινικές εκδηλώσεις όπως είναι η δακτυλίτιδα και η ενθεσίτιδα

✓ έχει εξαιρετικό προφίλ ασφαλείας που σχετίζεται και με τις ανοσορυθμιστικές δράσεις στα κύτταρα της έμφυτης ανοσίας


Спасибо
Gracias
شكرا
Obrigado
Спасибо
Dank U
Grazie
Ευχαριστώ
Danke
Dziękuję
Merci
Diolch
Obrigado
Ngiyabonga
Thank You
Dank U
Thank
Tack
You
Merci
תודה
Dziękuję
Danke
Grazie
Terima Kasih
Diolch
Grazie
Tack
Ευχαριστώ
Diolch
Gracias
Merci
Dank U
תודה