Καταστρώνοντας τη θεραπευτική στρατηγική στις φλεγμονώδεις αρθρίτιδες την εποχή των JAK αναστολέων

Πόσο εφικτή είναι η επίτευξη ύφεσης;

Νικόλαος Κούγκας, Ρευματολόγος
Δ΄Π/Θ Α.Π.Θ, Ιπποκράτειο Νοσοκομείο

Δήλωση συμφερόντων

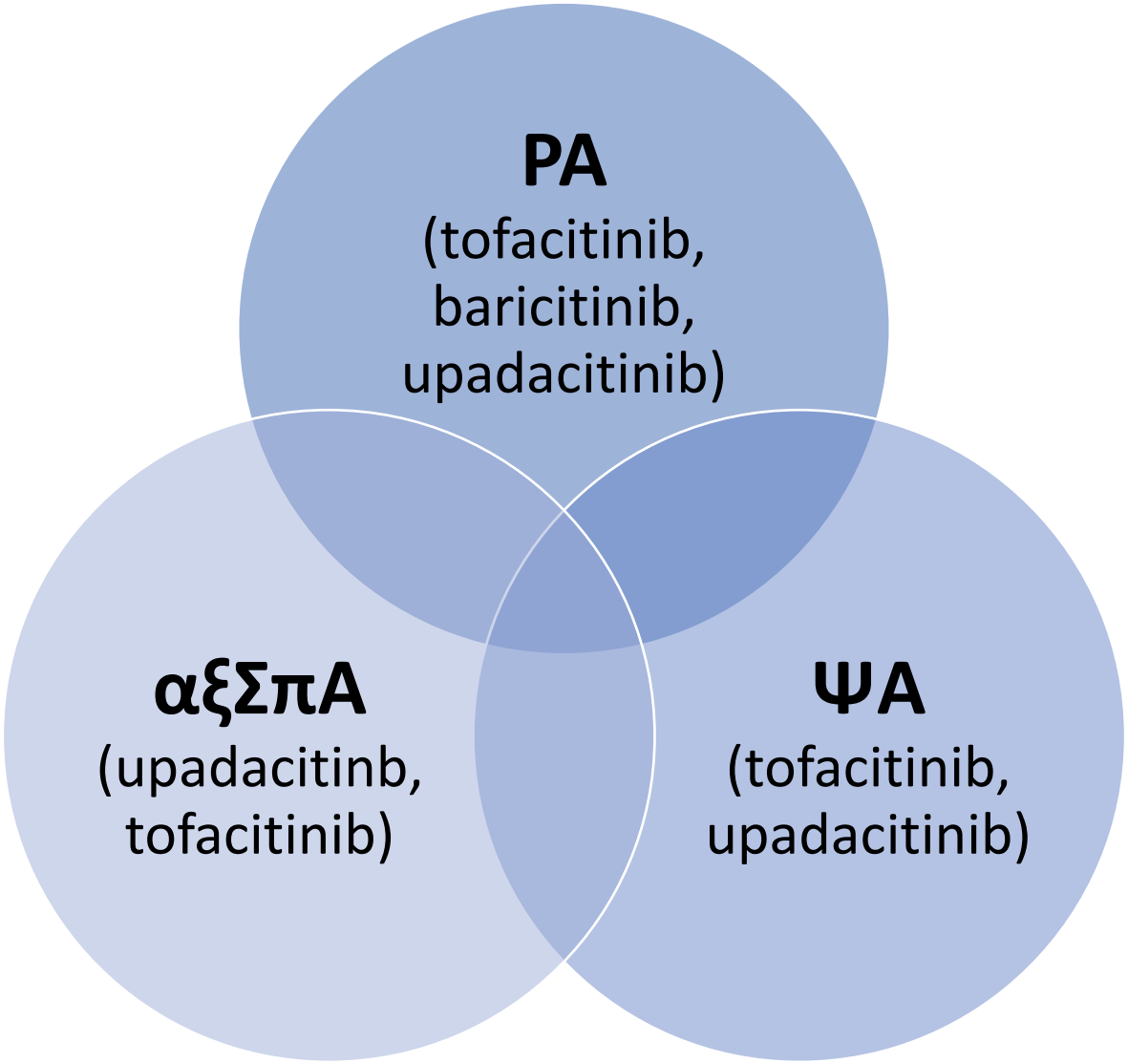
- Για τη συγκεκριμένη ομιλία έχω λάβει τιμητική αμοιβή από την Abbvie
- Τα τελευταία 2 έτη έχω λάβει τιμητική αμοιβή από τις εταιρείες Amgen, UCB, Pfizer, Genesis, Novartis, Roche, Pharmaserve-Lilly

Εισαγωγικά στοιχεία

- Ορισμός ύφεσης: απουσία ενεργότητας της νόσου
- Κατάσταση, όχι αλλαγή ή μετάβαση
- Προβλέπει την καλύτερη κλινική, λειτουργική και δομική εξέλιξη των φλεγμονωδών αρθριτίδων
- Ιδεατός στόχος στις κατευθυντήριες οδηγίες
- Ρευματοειδής αρθρίτιδα: Boolean, SDAI, CDAI, DAS 28 (??)
- Αξονική Σπονδυλοαρθρίτιδα: ASDAS ID
- Ψωριασική αρθρίτιδα: DAPSA, PASDAS

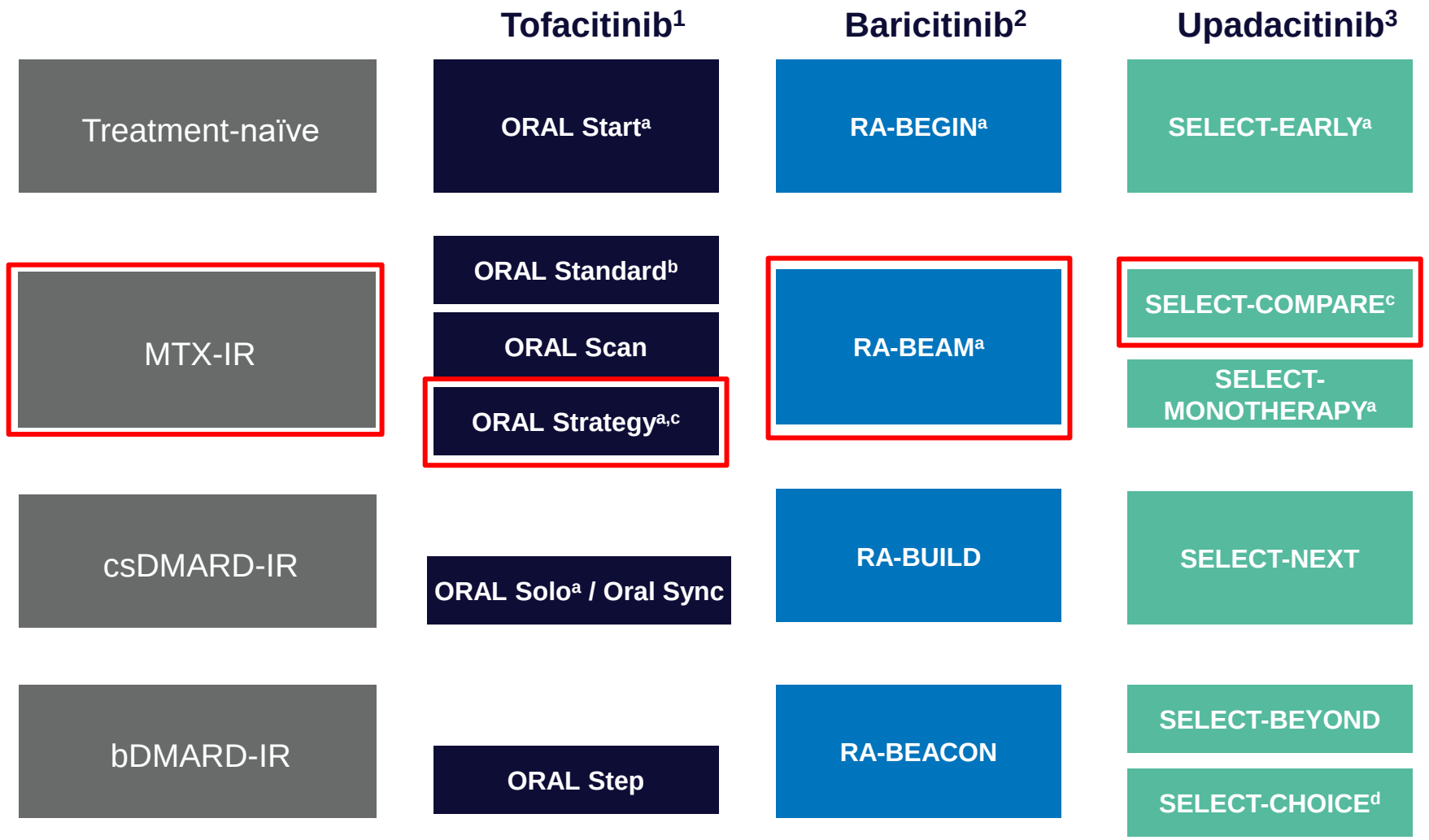
CDAI, Clinical Disease Activity Index; DAS28-CRP, Disease Activity Score with 28-joint count (C-reactive protein); SDAI, Simple Disease Activity Index; ASDAS ID, Ankylosing Spondylitis Disease Activity Score inactive disease; DAPSA, Disease Activity in PsA; PASDAS, PsA Disease Activity Score

JAK αναστολείς στις φλεγμονώδεις αρθρίτιδες



1. Tofacitinib SmPC. Available at: https://www.ema.europa.eu/en/documents/product-information/tofacitinib-epar-product-information_en.pdf ; 2. Baricitinib SmPC. Available at: https://www.ema.europa.eu/en/documents/product-information/baricitinib-epar-product-information_en.pdf ; 3. Upadacitinib SmPC. Available at: https://www.ema.europa.eu/en/documents/product-information/upadacitinib-epar-product-information_en.pdf

Κλινικές μελέτες φάσης III, σύγκρισης των JAK αναστολέων με το adalimumab σε ασθενείς με PA και ανεπαρκή ανταπόκριση στη MTX

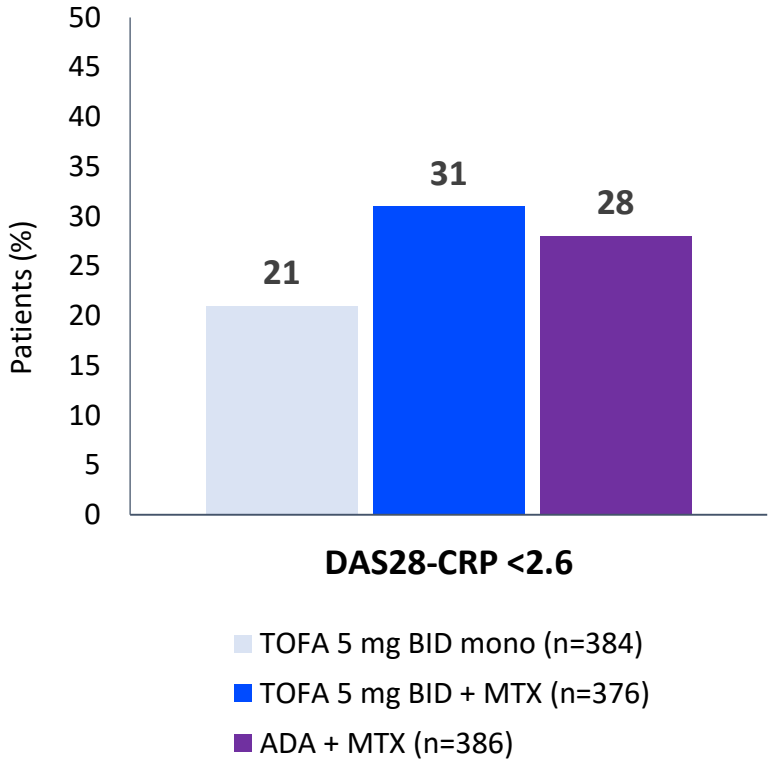


aTrials with a monotherapy arm; bTrial with adalimumab arm without formal statistical comparisons between adalimumab and tofacitinib; cTrials with statistical comparison of JAK inhibitor vs adalimumab in MTX-IR patients; dTrial with statistical comparison of JAK inhibitor vs abatacept in bDMARD-IR patients
b/csDMARD, biologic/conventional synthetic drug modifying antirheumatic drugs; IR, inadequate response; MTX, methotrexate

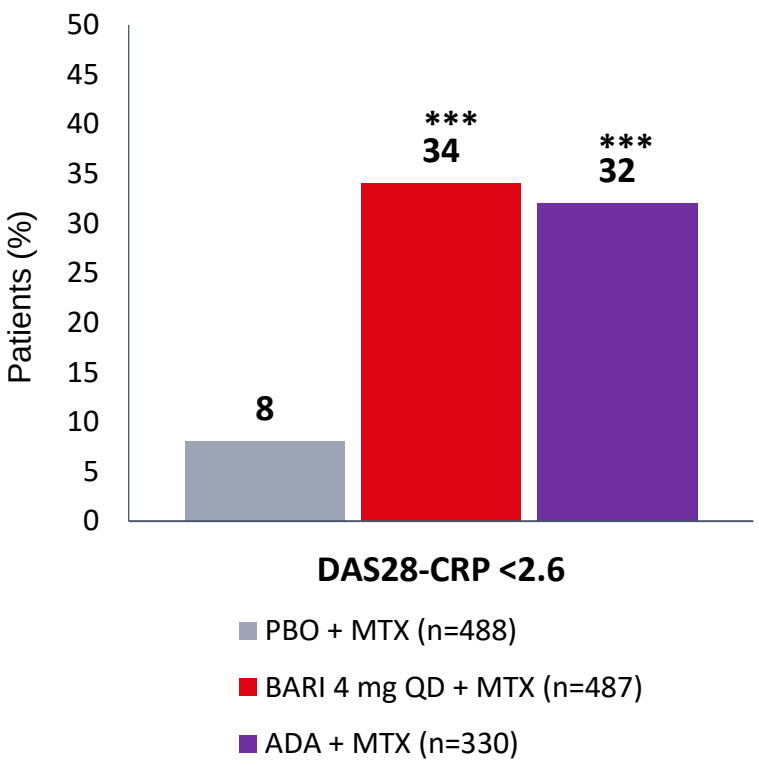
1. Tofacitinib SmPC. Available at: https://www.ema.europa.eu/en/documents/product-information/tofacitinib-epar-product-information_en.pdf ; 2. Baricitinib SmPC. Available at: https://www.ema.europa.eu/en/documents/product-information/baricitinib-epar-product-information_en.pdf; 3. Upadacitinib SmPC. Available at: https://www.ema.europa.eu/en/documents/product-information/upadacitinib-epar-product-information_en.pdf ; 4. Rubbert-Roth A, N Eng J Med 2020;383:1511–21

Το Upadacitinib είναι η πρώτη στοχευμένη θεραπεία με σημαντικά υψηλότερα ποσοστά ύφεσης έναντι του adalimumab

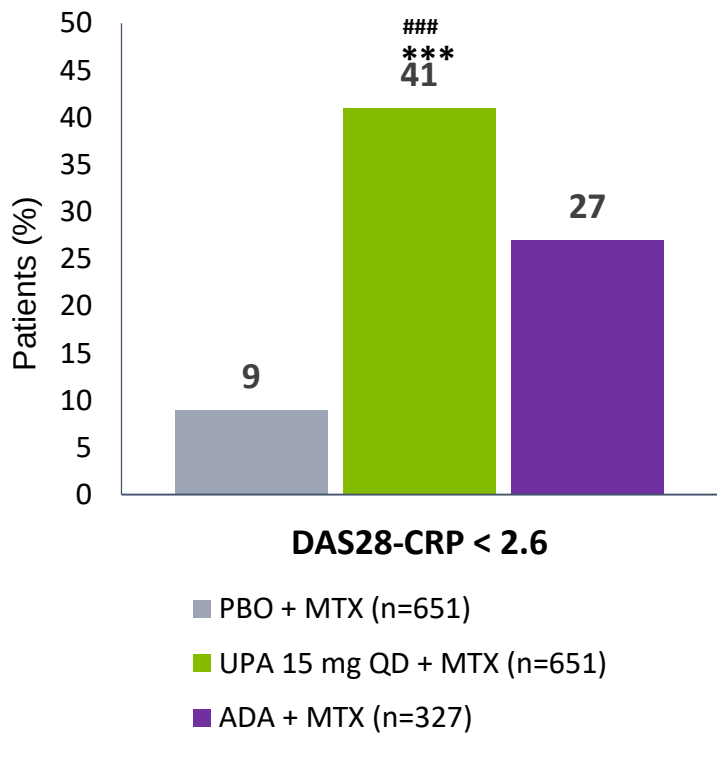
ORAL STRATEGY[1]



RA BEAM[2]



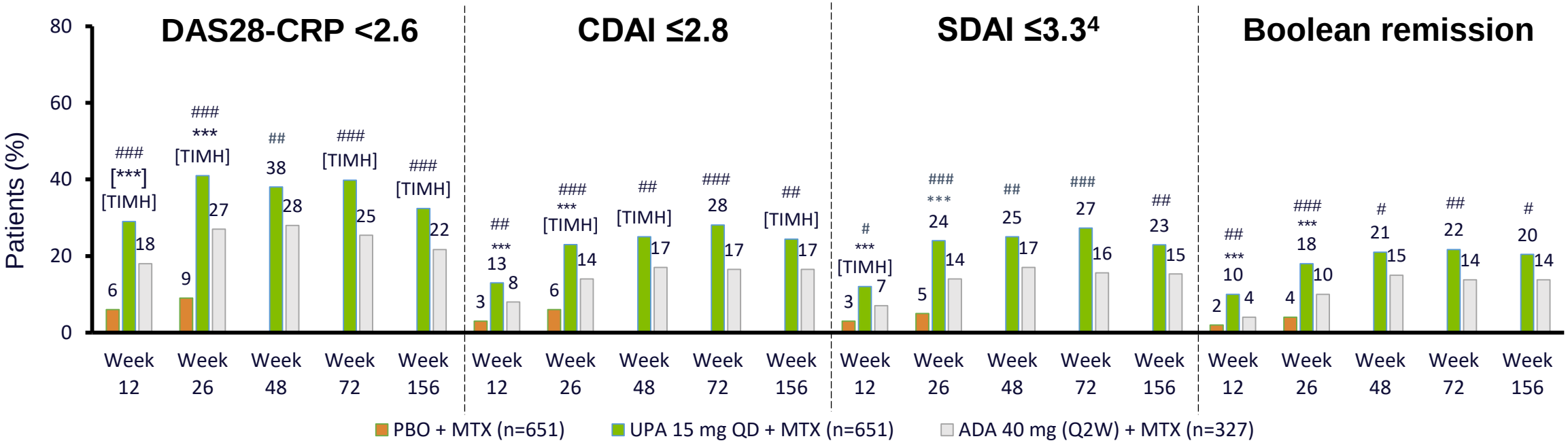
SELECT-COMPARE[3]



No head-to-head trials

1. Fleischmann R, et al. Lancet 2017;390:457–68. 2. Taylor PC, et al. N Engl J Med 2017;376:652–62. 3. Fleischmann R, et al. Arthritis Rheum (2019) 71 pp1788-1800

Σημαντικά υψηλότερα ποσοστά ασθενών στη μελέτη SELECT COMPARE πέτυχαν ύφεση με το UPA vs ADA, ανεξάρτητα από τον ορισμό της ύφεσης τις εβομάδες 12, 26,[1] 48,[2] 72,[3] και 156[3]

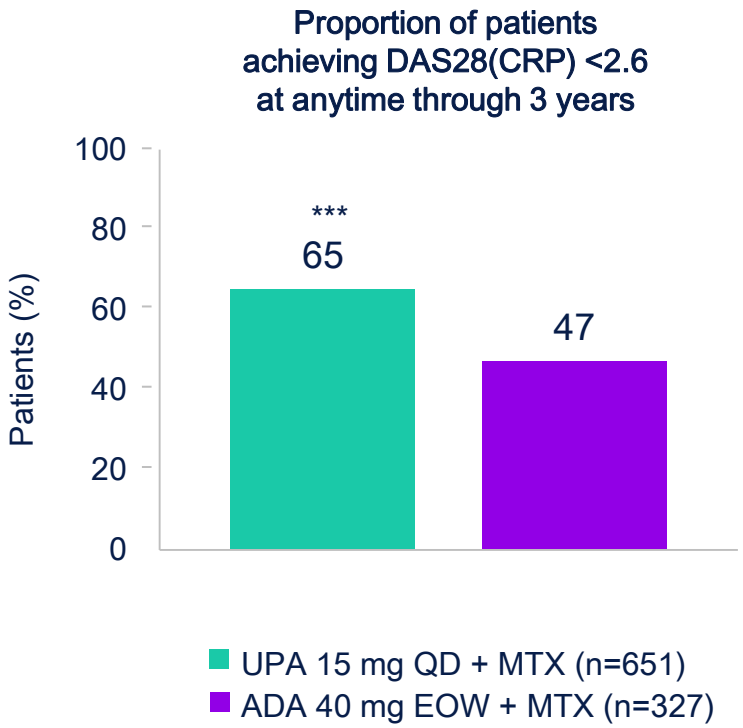


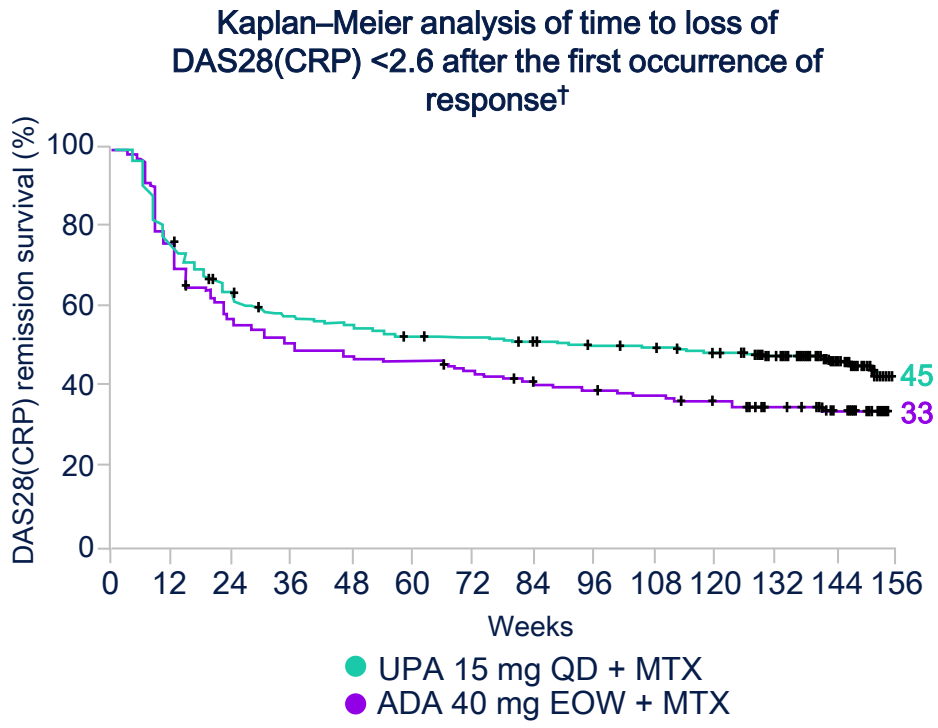
Comparisons adjusted for multiplicity: [***] p<0.001 vs PBO
Comparisons unadjusted for multiplicity: ***p<0.001 vs PBO; #p<0.05; ##p<0.01; ###p<0.001 vs ADA

ADA, adalimumab; CDAI, Clinical Disease Activity Index; CRP, C-reactive protein; DAS28-CRP, Disease Activity Score with 28-joint count (C-reactive protein); MTX, methotrexate; PBO, placebo; QD, once daily SDAI, Simple Disease Activity Index

1. Fleischmann R, et al. Arthritis Rheumatol 2019;71:1788–800;
2. Fleischmann R, et al. EULAR 2020 abstract [THU0201]; 3. Data on file. AbbVie. ABVRRTI72755;
4. Fleischmann R, et al. Arthritis Rheumatol 2019;71:1788–800:Suppl

Διατήρηση ύφεσης κατά DAS28(CRP) <2.6, από την πρώτη εμφάνιση έως την τελευταία επίσκεψη παρακολούθησης με UPA + MTX vs. ADA + MTX στη μελέτη SELECT COMPARE



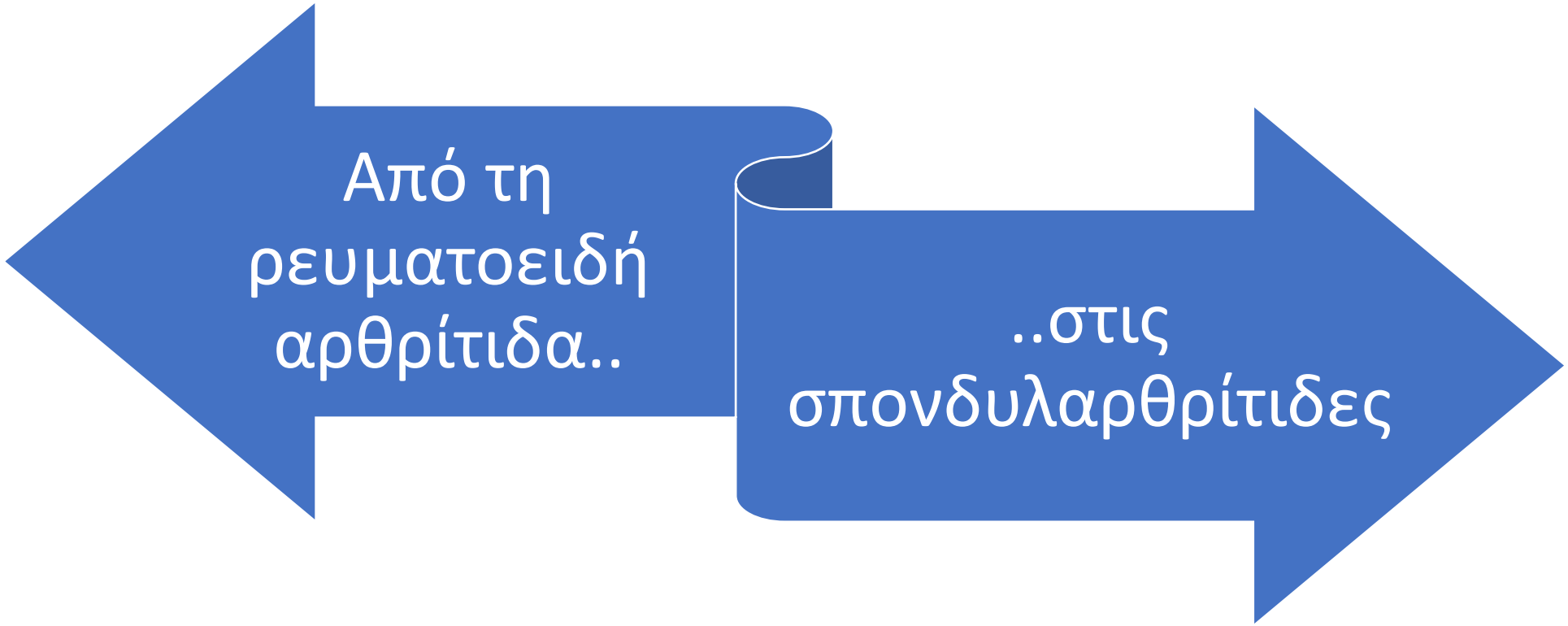


Sustained remission:

Time in which the response was first achieved to the earliest date at which response was lost at 2 continuous visits or discontinuation of study drug

Comparison not adjusted for multiplicity: ***nominal p<0.001 for UPA vs. ADA. †For patients who achieved remission, Kaplan–Meier was used to define the time from when the response was first achieved to the earliest date at which the response was lost at two consecutive visits, discontinuation of study drug, or loss of response at the time of rescue. Data were censored (e.g., data collection stopped) at 3 years, when all patients had reached the 156-week visit. Week 0 indicates the first occurrence of response. Treatment groups are by initial randomization; NRI was used for missing data. Patients on background MTX were randomized to receive UPA 15 mg QD, PBO, or ADA 40 mg EOW. Patients who did not achieve ≥20% improvements in TJC and SJC joint counts (Weeks 14–22) or LDA (CDAI ≤10) at Week 26 were rescued from UPA to ADA or PBO/ADA to UPA. ADA, adalimumab; CRP, C-reactive protein; DAS28, Disease Activity Score based on 28 joints; EOW, every other week; MTX, methotrexate; NRI, non-responder imputation; QD, once daily; RA, rheumatoid arthritis; UPA, upadacitinib.

Adapted from: Nash P, et al. ACR 2021. Poster 0837.


Από τη ρευματοειδή αρθρίτιδα..
..στις σπονδυλαρθρίτιδες

Οι JAK αναστολείς στη θεραπεία της αξΣπΑ

	r-axSpA			nr-axSpA
	TOFA Study Tofacitinib (Phase 3)[1]	**SELECT-AXIS 1 Upadacitinib (Phase 2/3)[2]**	**SELECT-AXIS 2 Upadacitinib (Phase 3)[3]**	**SELECT-AXIS 2 Upadacitinib (Phase 3)[3]**
Patients	**Majority bDMARD-naïve; ~1/5 TNFi-IR**	**bDMARD-naïve**	**bDMARD-IR**	**Majority bDMARD-naïve; ~1/3 bDMARD-IR**
Treatment arms	• TOFA 5 mg BID for 48 weeks • PBO for 16 weeks followed by TOFA 5 mg BID for 32 weeks	• UPA 15 mg QD for 104 weeks • PBO for 14 weeks followed by UPA 15 mg QD for 90 weeks	• UPA 15 mg QD for 104 weeks • PBO for 14 weeks followed by UPA 15 mg QD for 90 weeks	• UPA 15 mg QD for 104 weeks • PBO for 52 weeks followed by UPA 15 mg QD for 52 weeks
Sample size, N	269	187	420	314
Primary endpoint	ASAS20 at Week 16	ASAS40 at Week 14	ASAS40 at Week 14	ASAS40 at Week 14

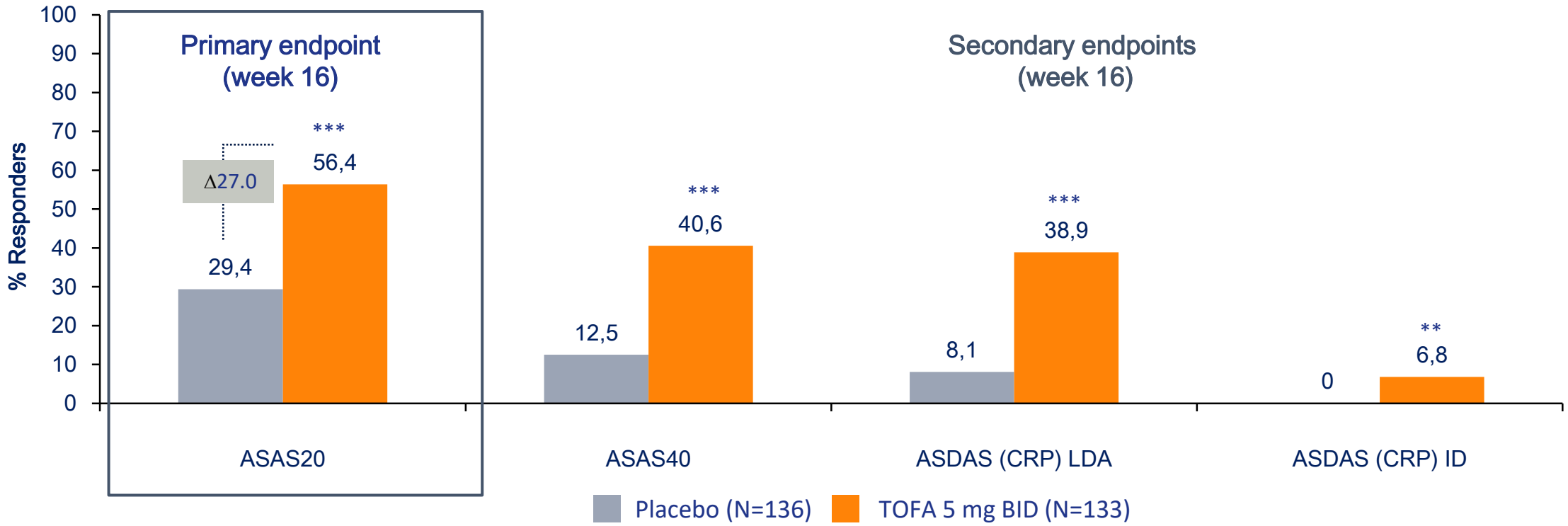
Filgotinib phase 2 trial (TORTUGA)[4] met primary endpoint, but phase 3 program was not pursued

Tofactinib (TOFA) and Filgotinib (FILGO) do not have regulatory approval for non-radiographic axial spondyloarthritis (nr-axSpA).

ASDAS, Ankylosing Spondylitis Disease Activity Score; ASAS20/40, 20%/40% improvement in Assessment in Ankylosing Spondylitis response criteria; bDMARD, biologic disease-modifying anti-rheumatic drug; BID, twice a day; IR, inadequate response; JAK, Janus kinase; MRI, magnetic resonance imaging; NSAID, non-steroidal anti-inflammatory drug; PBO, placebo; QD, once a day; SIJ, sacroiliac joint; SPARCC, Spondyloarthritis Research Consortium of Canada; TNFi, tumour necrosis factor inhibitor; UPA, upadacitinib.

1. Deodhar A, et al. Ann Rheum Dis. 2021;annrheumdis-2020-219601;
2. van der Heijde D, et al. Lancet 2019;394:2108–2117;
3. van den Bosch EULAR 2022 OP0016;
4. van der Heijde D, et al. Lancet 2018;392:2378–2387

Tofacitinib vs. Placebo στην ΑΣ (16 εβδ.)



**p<0.01, ***p<0.001
ASAS20, 20% improvement in Assessment in Ankylosing Spondylitis response criteria; BID, twice a day; bMARD, biologic disease-modifying antirheumatic drug; CRP, c-reactive protein; ID, inactive disease (<1.3); IR, inadequate response; LDA, low disease activity (<2.1); TOFA, tofacitinib; TNFi, tumor necrosis factor inhibitor.

Adapted from:
1. Deodhar A, et al. Ann Rheum Dis. 2021; 80(8):1004-1013.

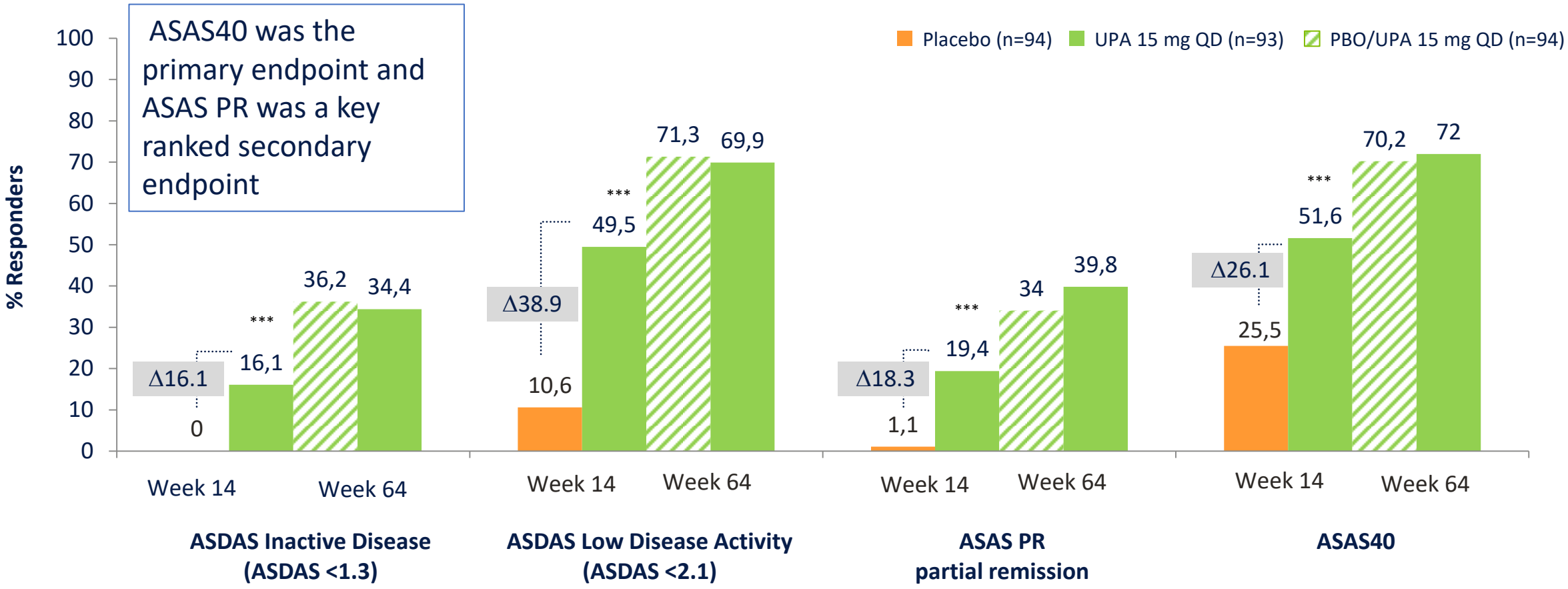
Το Upadacitinib στην αξΣπΑ

	SELECT-AXIS 1[1]	SELECT-AXIS 2 Study 1[2]	SELECT-AXIS 2 Study 2[3]
	SELECT-AXIS 1 Upadacitinib	SELECT-AXIS 2 Upadacitinib	SELECT-AXIS 2 Upadacitinib
Patients	bDMARD-naïve AS	bDMARD-IR AS	nr-axSpA (bDMARD-naïve and bDMARD-IR)
Treatment arms	• UPA 15 mg QD for 104 weeks • PBO for 14 weeks followed by UPA 15 mg QD for 90 weeks	• UPA 15 mg QD for 104 weeks • PBO for 14 weeks followed by UPA 15 mg QD for 90 weeks	• UPA 15 mg QD for 104 weeks • PBO for 52 weeks followed by UPA 15 mg QD for 52 weeks
Sample size, N	187 ✓	420 ✓	314 ✓
Primary endpoint	ASAS40 at Week 14	ASAS40 at Week 14	ASAS40 at Week 14

AS, ankylosing spondylitis; ASAS40, ≥40% improvement in Assessment of SpondyloArthritis International Society; axSpA, axial spondyloarthritis; b, biologic; DMARD, disease-modifying anti-rheumatic drug; IR, inadequate response; nr, non-radiographic; NSAID, non-steroidal anti-inflammatory drug; PBO, placebo; QD, once daily; UPA, upadacitinib.

Adapted from:
1. van der Heijde D, et al. Lancet 2019;394(10214):2108–2117.
2. Van der Heijde D, et al. EULAR 2022 Abstract No. 2518;
3. Doedhar A, et al. EULAR 2022 Abstract No. 2534.

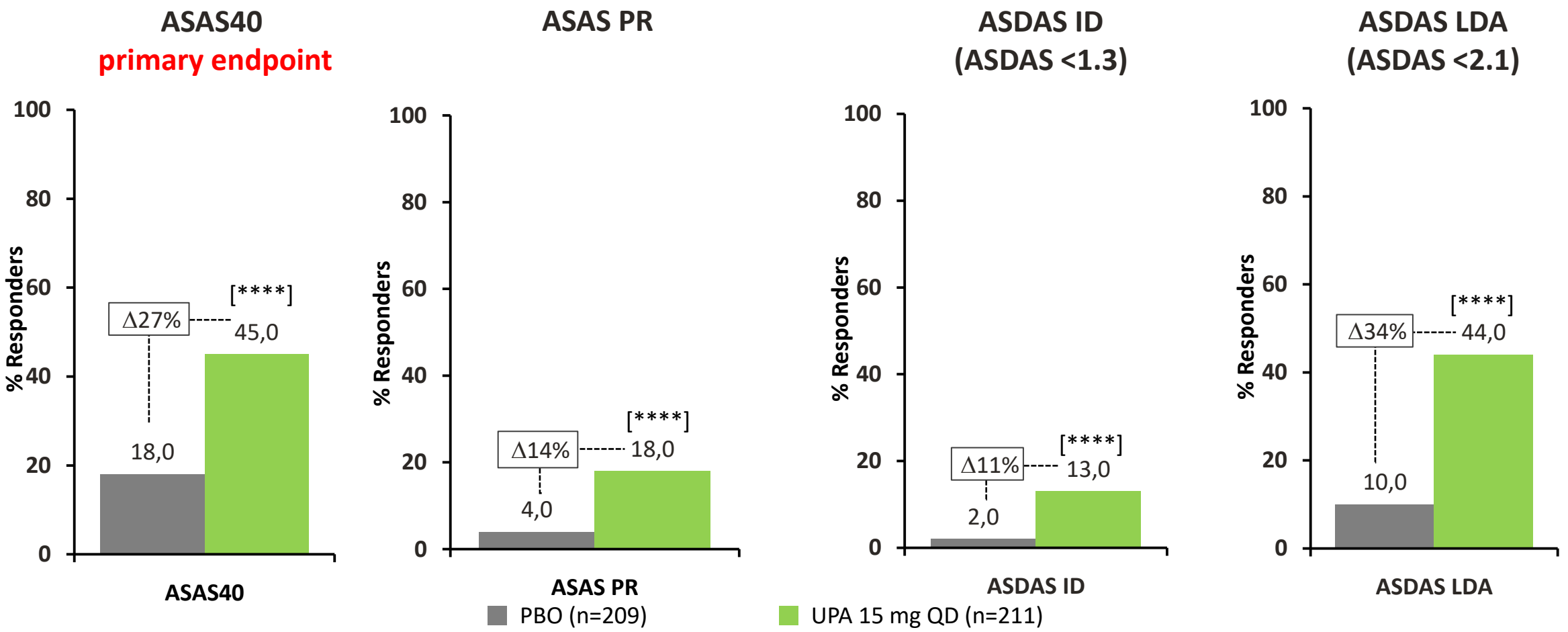
Επίτευξη αυστηρών δεικτών ενεργότητας νόσου υπό upadacitinib τις εβδομάδες 14[1] και 64[2] (NRI) σε bDMARD-naïve ασθενείς με ΑΣ



Comparisons not adjusted for multiplicity: nominal *** p<0.001 for UPA vs placebo.
ASAS, Assessment of SpondyloArthritis International Society; BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; ASDAS, Ankylosing Spondylitis Disease Activity Score;
NRI, non-responder imputation; PBO, placebo; PR, partial remission; QD, once daily; UPA, upadacitinib.

1. van der Heijde D et al. Lancet 2019;394(10214):2108–2117;
2. Deodhar A, et al. Arthritis Rheumatol. 2021 Jul 1. doi: 10.1002/art.41911

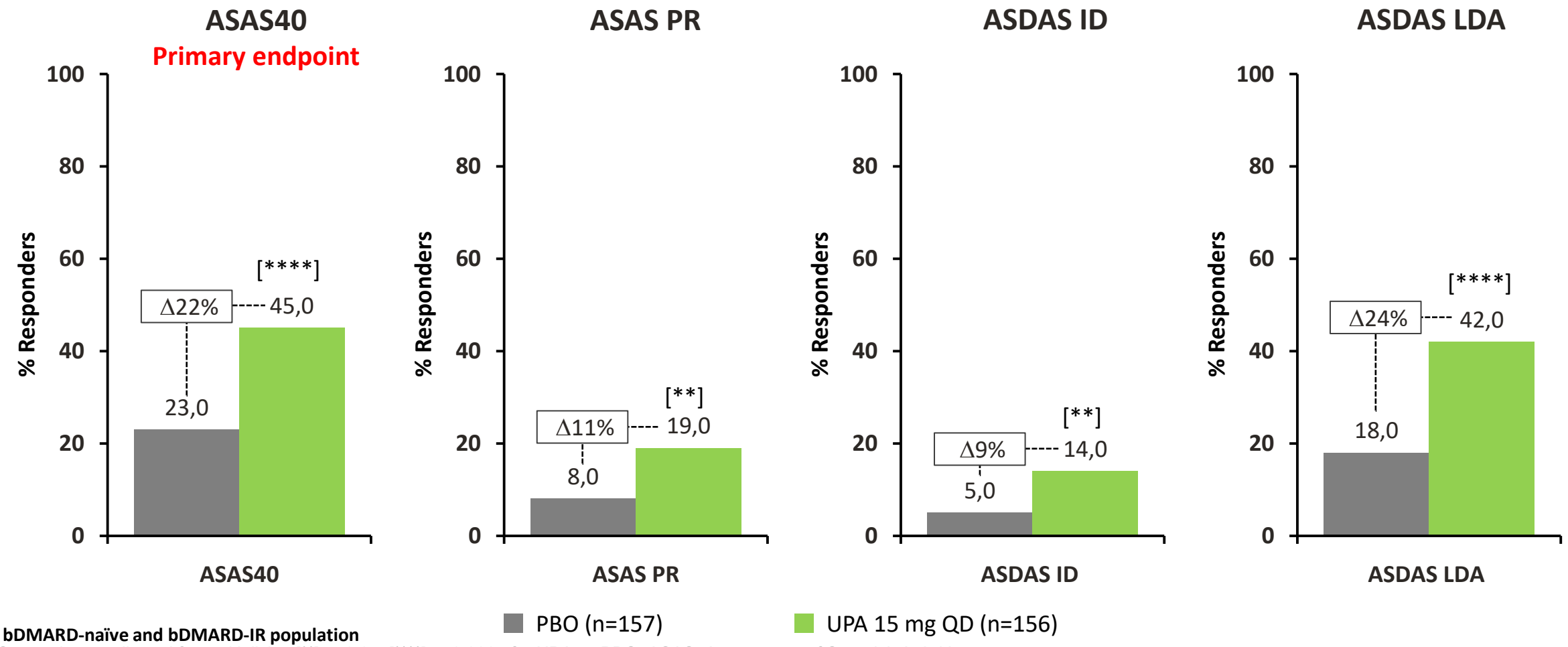
Σημαντικά περισσότεροι ασθενείς πέτυχαν αυστηρούς δείκτες ενεργότητας νόσου με το UPA vs PBO σε bDMARD-IR ασθενείς με ΑΣ την εβδομάδα 14 (NRI)



Comparisons adjusted for multiplicity: [****] p<0.0001 for UPA vs PBO. ASAS, Assessment of SpondyloArthritis International Society; ASAS40, ≥40% improvement in Assessment of SpondyloArthritis International Society; ID, inactive disease; LDA, low disease activity; MI, major improvement;
NRI, non-responder imputation; PBO, placebo; PR, partial remission; QD, once daily; UPA, upadacitinib.

van der Heijde D et al. Ann Rheum Dis 2022

Σημαντικά περισσότεροι ασθενείς με μη ακτινολογικά επιβεβαιωμένη αξΣπΑ πέτυχαν αυστηρούς δείκτες ενεργότητας νόσου με το UPA vs PBO την εβδομάδα 14 (NRI)



bDMARD-naïve and bDMARD-IR population

Comparisons adjusted for multiplicity: [**] p<0.01, [****] p<0.0001 for UPA vs PBO. ASAS, Assessment of SpondyloArthritis International Society;

ASAS40, ≥40% improvement in Assessment of SpondyloArthritis International Society; ASDAS, Ankylosing Spondylitis Disease Activity Score; axSpA, axial spondyloarthritis; ID, inactive disease; LDA, low disease activity; nr, non-radiographic; NRI, non-responder imputation; PBO, placebo; PR, partial remission; QD, once daily; UPA, upadacitinib.

Deodhar A., et al. EULAR 2022 Oral presentation OP0016

Οι JAK αναστολείς στη θεραπεία της ΨΑ

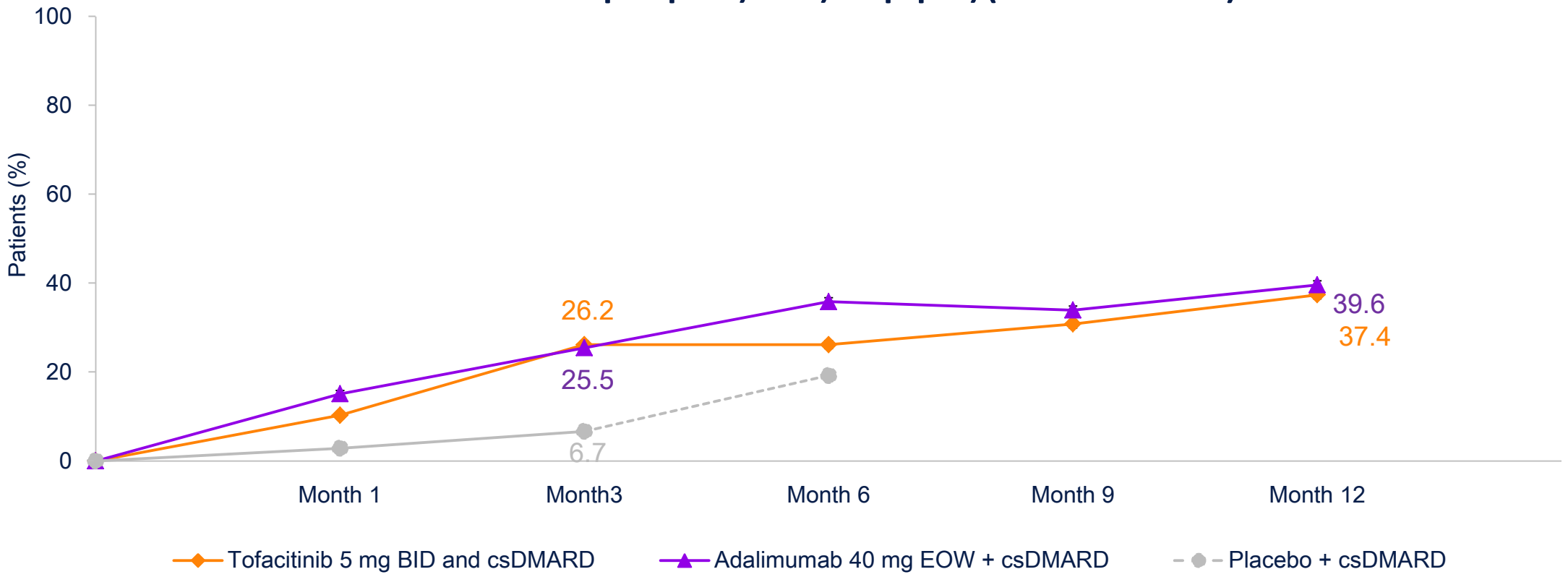
	Tofacitinib[1,2]		Upadacitinib[3,4]	
Study	**OPAL BROADEN[1]**	**OPAL BEYOND[2]**	**SELECT-PsA 1[3]**	**SELECT-PsA 2[4]**
Population	Non-bDMARD-IR	TNF-IR	Non-bDMARD-IR	bDMARD-IR
Active comparator	Adalimumab	None	Adalimumab	None
Dose	TOFA 5 mg BID TOFA 10 mg BID Placebo ADA 40 mg EOW	TOFA 5 mg BID TOFA 10 mg BID Placebo	UPA 15 mg QD UPA 30 mg QD Placebo ADA 40 mg EOW	UPA 15 mg QD UPA 30 mg QD Placebo
1º endpoint	ACR20 vs PBO at month 3 & ΔHAQ-DI score at month 3	ACR20 vs PBO at month 3 & ΔHAQ-DI score at month 3	ACR20 vs PBO at Week 12	ACR20 vs PBO at Week 12
Sample size	n=422	n=395	n=1705	n=642

ACR20, American College of Rheumatology 20% improvement score; ADA, adalimumab; b, biologic; DMARD, disease-modifying anti-rheumatic drug; EOW, every other week; IR, inadequate response; OLE, open-label extension; PBO, placebo; PsA, psoriatic arthritis; QD, once daily; UPA, upadacitinib; TNF, tumor necrosis factor

1. Mease P, et al. N Engl J Med. 2017;377(16):1537-1550
2. Gladman et al. N Engl J Med 2017; 377:1525-1536
3. McInnes IB et al. N Engl J Med 2021;384(4):1227–1239;
4. Mease PJ et al. Ann Rheum Dis 2021;80:312–320.

Το Tofacitinib σε bDMARD-naïve ασθενείς με ΨΑ

MDA ανταπόκριση έως τους 12 μήνες (OPAL Broaden)[1,2]

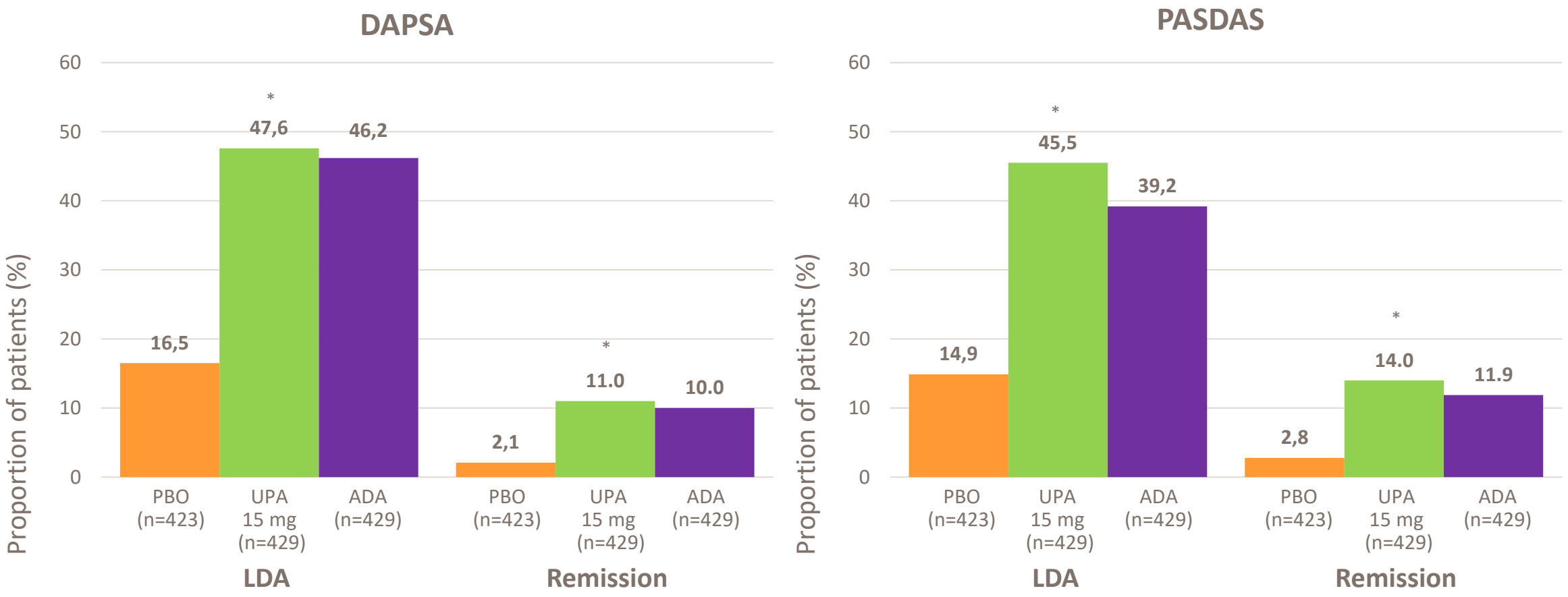


The data represent the complete set for analysis, the missing values being compensated as the absence of response to treatment.

ADA, adalimumab; BID, 2 times per day; bDMARD, biologic disease-modifying anti-rheumatic drug; csDMARD, conventional synthetic disease modifying antirheumatic drug; MDA, minimal disease activity; OPAL, Oral Psoriatic Arthritis Trial; PsA, Psoriatic arthritis; EOW, every 2 weeks.

Adapted from: 1. Mease P, et al. N Engl J Med. 2017;377(16):1537-1550;
2. Mease P, et al. N Engl J Med. 2017;377(16):1537-1550 (Supplementary Data).

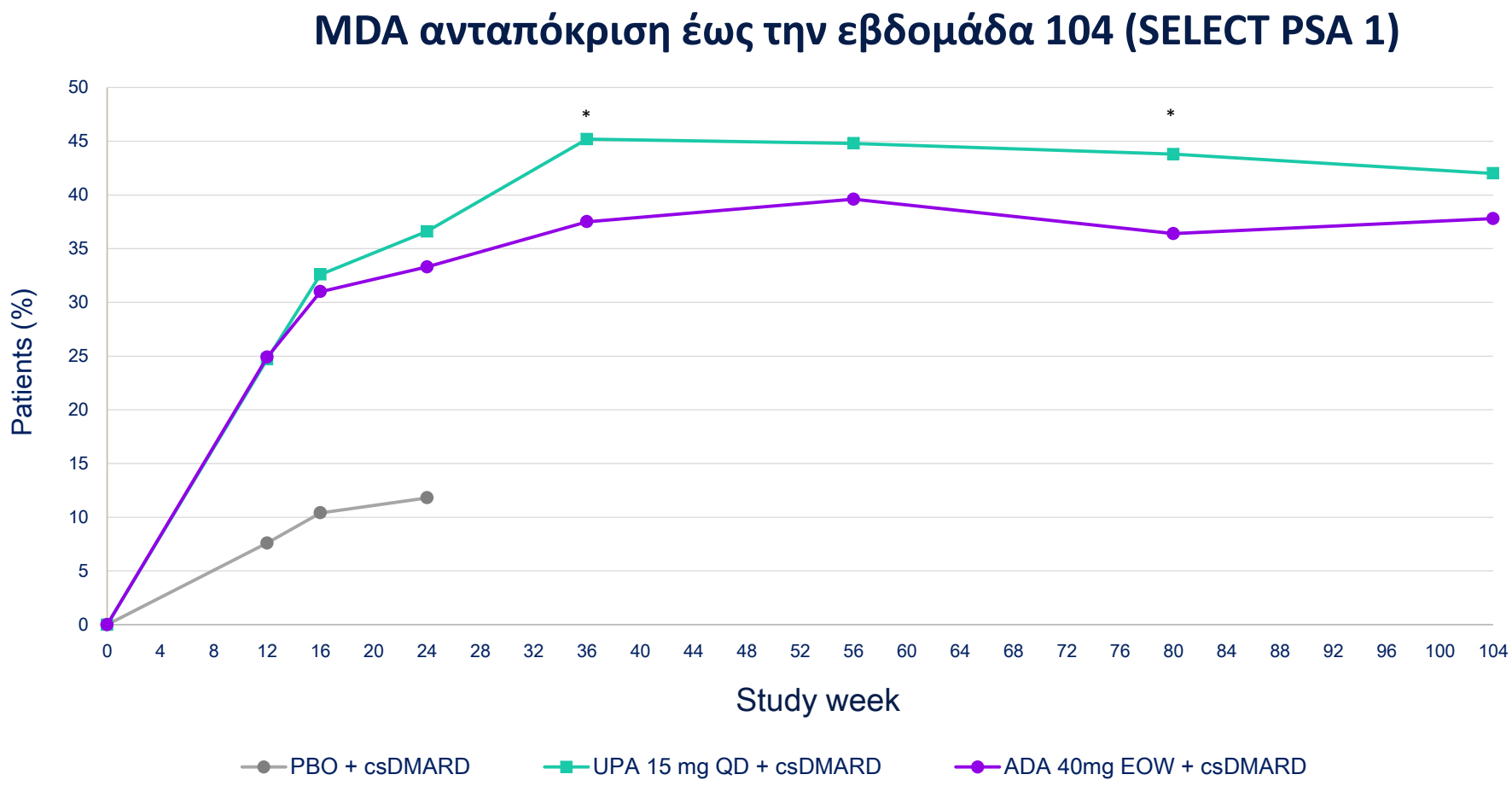
Το Upadacitinib παρουσίασε αριθμητικές διαφορές vs adalimumab στους δείκτες DAPSA και PASDAS την εβδομάδα 24 (NRI) στη μελέτη SELECT PsA 1



Comparisons not adjusted for multiplicity: *p<0.05 for UPA vs PBO.
Remission and LDA were defined as DAPSA scores of ≤4/≤14, and PASDAS scores of ≤1.9/≤3.2, respectively. ADA, adalimumab; DAPSA, Disease Activity in PsA; LDA, low disease activity; NRI, non-responder imputation; PASDAS, PsA Disease Activity Score; PBO, placebo; PsA, psoriatic arthritis; UPA, upadacitinib.

Mease P et al. Arthritis Rheumatol 2020;72(Suppl 10).

Το Upadacitinib αριθμητικά υψηλότερη ανταπόκριση κατά MDA συγκριτικά με το ADA την εβδομάδα 104



Data were analyzed using Cochran-Mantel-Haenszel tests with non-responder imputation and are shown as response rates with 95% CIs. *p<0.05, **p<0.01, ***p<0.001, ****p<0.0001 UPA 15 versus ADA. nominal p-values are shown and were not multiplicity controlled. ACR70, ≥ 70% improvement in American College of Rheumatology response criteria; ADA, adalimumab; bDMARD, biologic disease modifying antirheumatic drug; CI, confidence interval; csDMARD, conventional synthetic disease modifying antirheumatic drug; EOW, every other week; MDA, Minimal disease activity; QD, once daily; UPA, upadacitinib.

Adapted from: 1. McInnes I, et al. Long-term Efficacy and Safety of Upadacitinib in Patients With Psoriatic Arthritis: 2-Year Results From the Phase 3 SELECT-PsA 1 Study. In: European Congress of Rheumatology (EULAR); 2022.

Συμπεράσματα

- Επιθυμητός στόχος η ύφεση όχι μόνο στις κλινικές μελέτες αλλά και στην καθημερινή κλινική πράξη
- Εφικτός στόχος στις φλεγμονώδεις αρθρίτιδες σε ασθενείς υπό θεραπεία με JAKi και ιδιαίτερα με το upadacitinib, ανεξάρτητα από την προηγηθείσα αγωγή
- Αναπάντητα ερωτήματα
  - Κόπωση, PRO’s
  - Διάρκεια της ύφεσης
  - Οι υπόλοιποι ασθενείς που δεν επιτυγχάνουν την ύφεση