«Πότε μεγιστοποιείται το όφελος με την χρήση των JAKis στη PA;»

Νέστορας Αυγουστίδης, Ρευματολόγος, Επιμελητής Α', ΠΑΓΝΗ

Για την ομιλία θα υπάρχει τιμητική αμοιβή από την εταιρία ΦΑΡΜΑΣΕΡΒ-LILLY

Presentation outlines

- Three case presentations of different RA patients treated with Baricitinib

Clinical case

- 40 years old female , six months history of seropositive , CCP (+), RF(-) RA
- Comorbidities : past smoking history, BMI=28 Kg/m²
- Family history: mother RA
- Occupation: Business executive
- Initial assessment: ESR=40, CRP=1.5 <0.5 mg/dl, SJC=6, TJC=5, VAS=60 , CDAI=23, DAS-28 (ESR)=5.36, HAQ- DI=0.88
- X-rays= (-) erosions
- Initially treated with Prednisolone 7.5 mg/day with tapering to 5 mg/day and methotrexate 15 mg /week with gradual dose escalation to 20 mg/week .

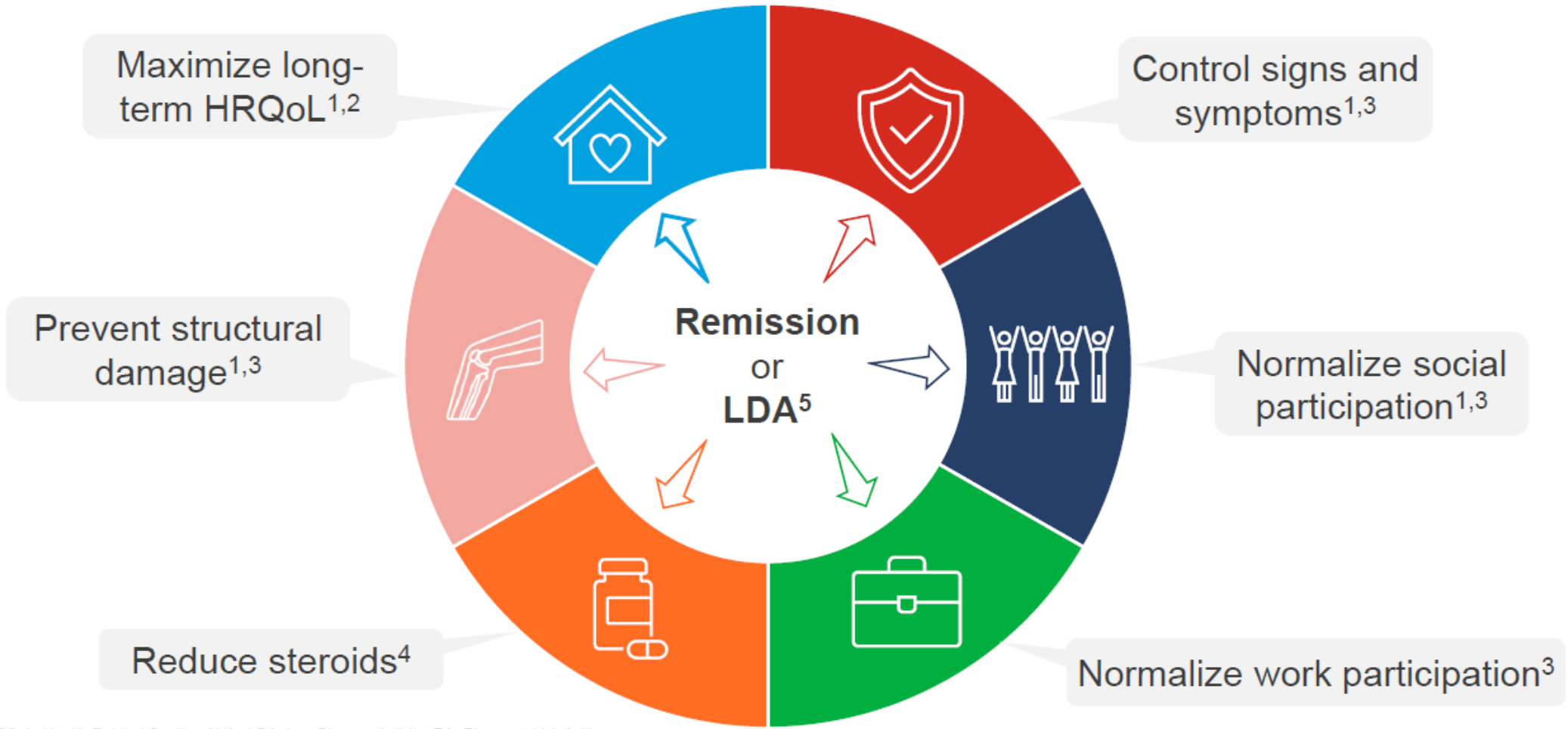
- In the clinical and laboratory assessment four months since diagnosis still on HDA: treatment at this stage Prednisolone 5 mg/day and methotrexate 20 mg orally /week
- ESR=35, CRP=1.2<0.5 ,TJC=7, SJC=4, VAS=50, CDAI, DAS-28(ESR)= 5.23, CDAI=23, HAQ-DI=0.86
- After discussion with patient Baricitinib 4 mg/day was initiated

Clinical case

- In the clinical and laboratory assessment four months after BARI initiation:
- Patient was off steroids
- She was still on methotrexate 20 mg/day orally
- ESR=15, CRP=0.6 <0.5 ,TJC=1, SJC=1, VAS=20, CDAI=, DAS-28(ESR)= 3.02, CDAI=6, LDA
- HAQ-DI=0.25

- Good EULAR Response : change in DAS28(ESR)=2.21> 1.2 and DAS28<3.2
- Change in HAQ: 0.61
- MCID:0.25

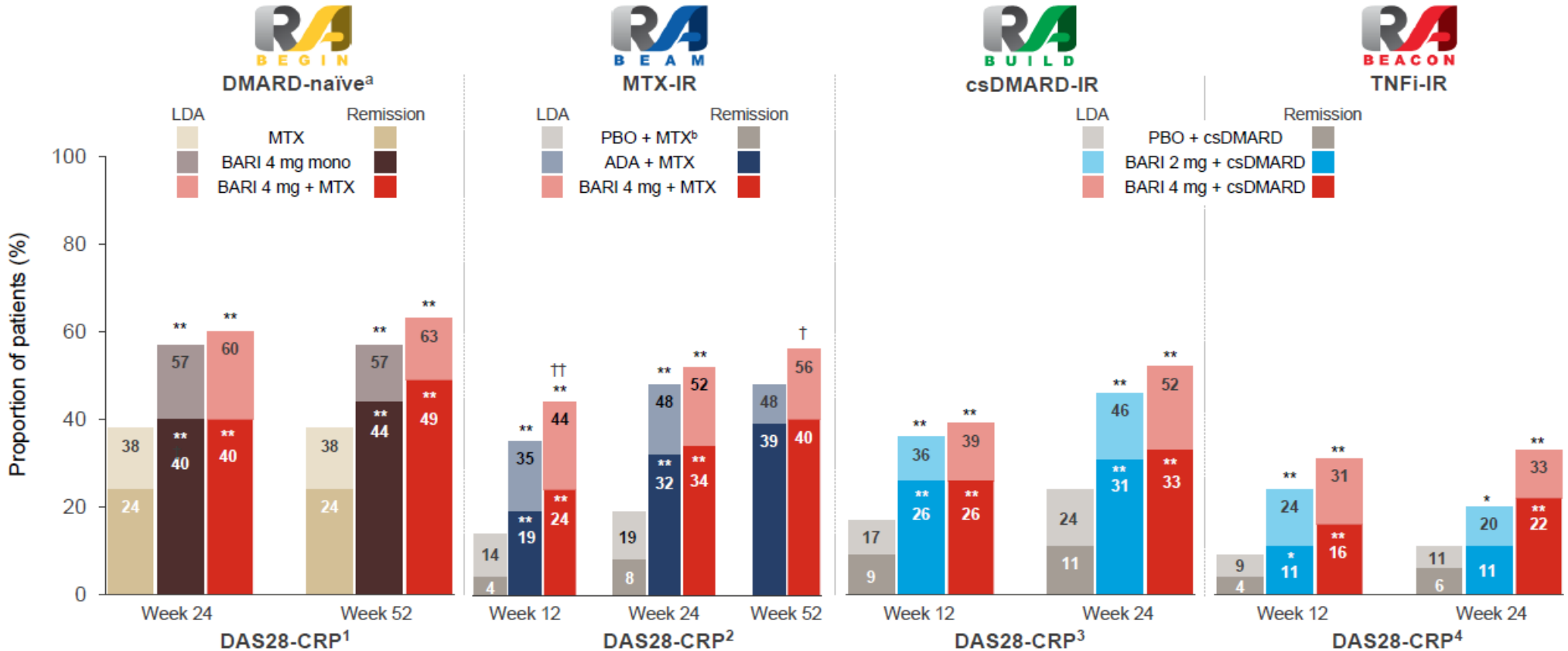
Treatment Goals in RA



HRQoL=Health-Related Quality of Life; LDA=Low Disease Activity; RA=Rheumatoid Arthritis.

1. Solomon DH, et al. Arthritis Rheumatol. 2014;66(4):775–82. 2. Scott IC, et al. RMD Open. 2016;2:e000270. 3. Smolen JS, et al. Ann Rheum Dis. 2020;79(6):685–99.
4. Hua C, et al. RMD Open. 2020;6:e000536. 5. Smolen JS, et al. Ann Rheum Dis. 2023;82(1):3–18.

RCTs Demonstrated the Efficacy of Baricitinib Across Clinically Relevant Patient Populations



*p≤0.05; **p≤0.001 vs. MTX and PBO. †p≤0.05; ††p≤0.01 vs. ADA. [a]Use in MTX-naïve population was off-label. [b]Patients receiving PBO were switched to BARI 4 mg at Week 24.
ADA=Adalimumab; BARI=Baricitinib; csDMARD=Conventional Synthetic DMARD; DAS28-CRP=Disease Activity Score 28 for Rheumatoid Arthritis with C-Reactive Protein; DMARD=Disease-Modifying Anti-Rheumatic Drug; IR=Inadequate Responder; LDA=Low Disease Activity; Mono=Monotherapy; MTX=Methotrexate; PBO=Placebo; RCT=Randomized Controlled Trial; TNFi=Tumor Necrosis Factor Inhibitor.

1. Fleischmann R, et al. Arthritis Rheumatol. 2017;69(3):506–17. 2. Taylor PC, et al. N Engl J Med. 2017;376(7):652–62 (incl. Suppl.). 3. Dougados M, et al. Ann Rheum Dis. 2017;76(1):88–95 (incl. Suppl.).
4. Genovese MC, et al. N Engl J Med. 2016;374(13):1243–52 (incl. Suppl).

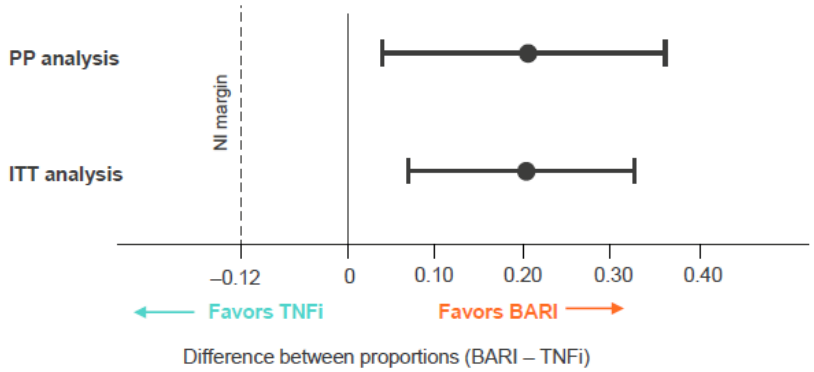
Baricitinib Was Non-Inferior and Statistically Superior to TNFi in ACR 50 Response at Week 12[1]

PERFECT-RA Study

Treatment Response

- At 12 weeks, the lower bound of the 95% Wilson score CI for the difference in proportion of patients meeting ACR 50 was above the –12% NI margin and to the right of zero in both the PP and ITT analyses; hence, baricitinib was found to be **not only non-inferior but also statistically superior to TNFi**

Difference in Proportion of Patients Achieving ACR 50 at Week 12[a]



ITT population

Comprised all subjects who correctly enrolled in the study

PP population

Excluded all subjects who met either of the following criteria:

- Discontinued the study
- Missing data for ≥1 assessment of the primary outcome (ACR 50) at baseline or 12 weeks

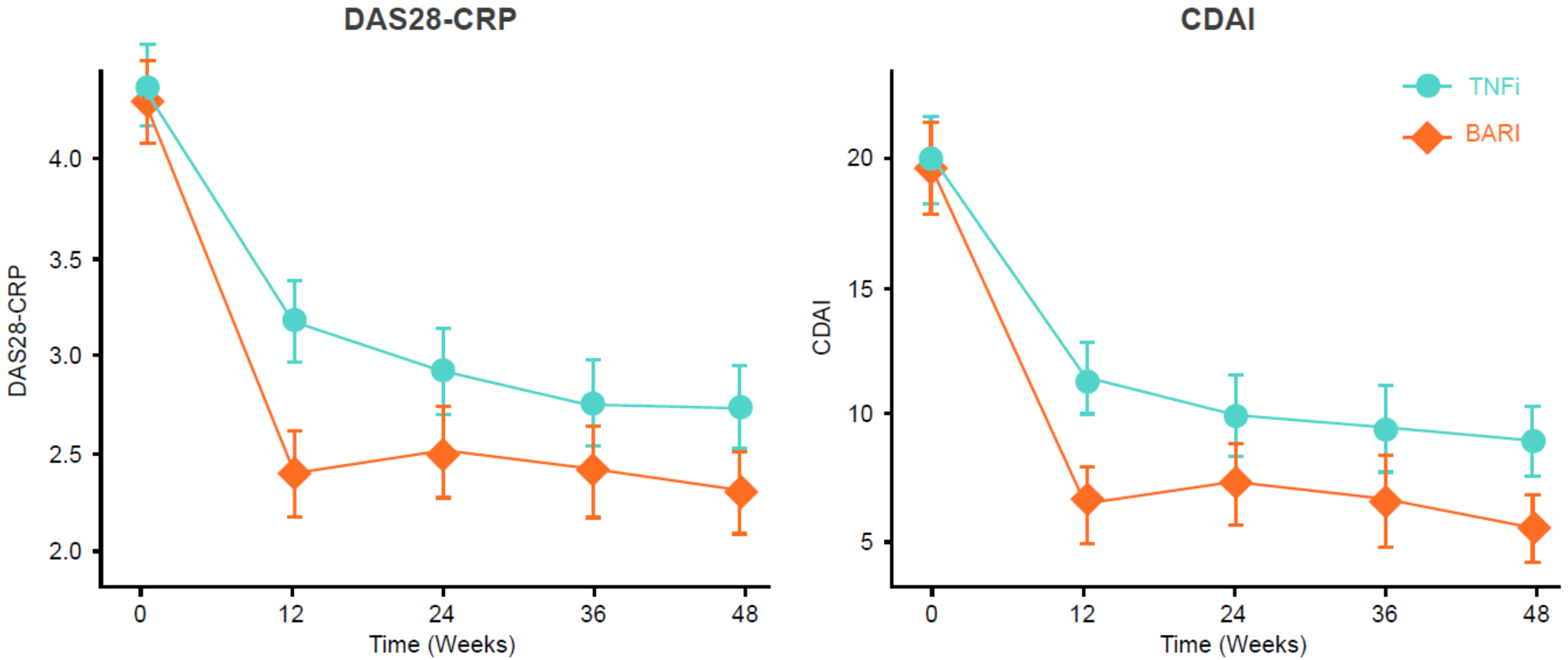
[a]The NI margin of 12% was based on previous studies in the RA population, including the RA-BEAM study.[1,2]
ACR 50=50% Improvement in the American College of Rheumatology Scale Score; BARI=Baricitinib; CI=Confidence Interval; ITT=Intention-to-Treat; NI=Non-Inferiority; PP=Per-Protocol; RA=Rheumatoid Arthritis; TNFi=Tumor Necrosis Factor Inhibitor.

1. van de Laar CJ, et al. RMD Open. 2024;10(2):e004291 (incl. Suppl.). 2. Taylor PC, et al. N Engl J Med. 2017;376(7):652–62.

Primary endpoint non inferiority and if so ACR50 response at week 12 (42% vs 20%).
DAS28-CRP <2.6 at week 12 compared (75 % vs 46%) of TNFi patients.

Baricitinib Led to a More Rapid Decline in DAS28-CRP and CDAI Scores[1]

PERFECT-RA Study

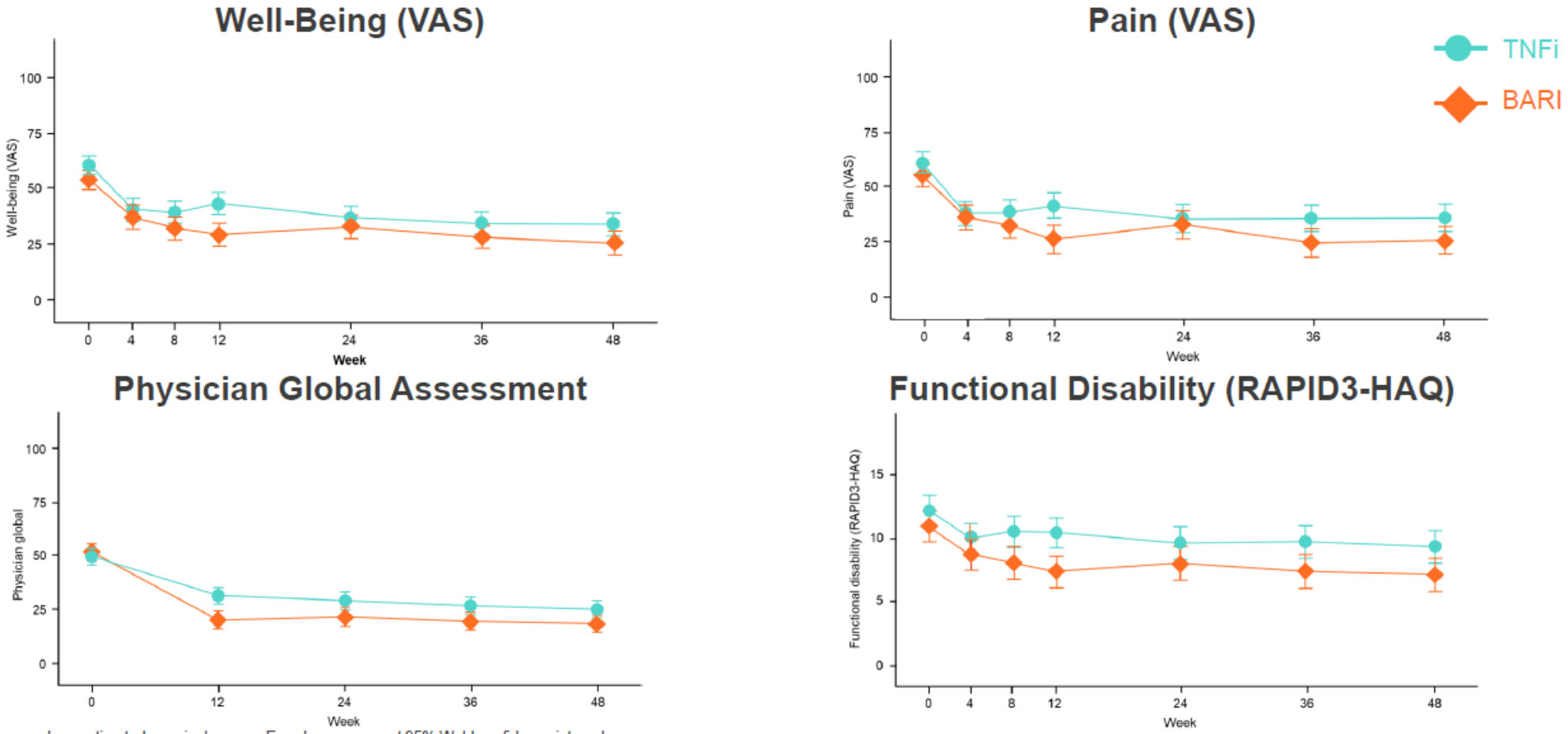


Figures show estimated marginal means. Error bars represent 95% Wald confidence interval.
BARI=Baricitinib; CDAI=Clinical Disease Activity Index; DAS28-CRP=Disease Activity Score 28 for Rheumatoid Arthritis with C-Reactive Protein; TNFi=Tumor Necrosis Factor Inhibitor.

1. van de Laar CJ, et al. RMD Open. 2024;10(2):e004291 (incl. Suppl.).

Improvements in Patient-Reported Outcomes Were in Favor of Baricitinib Treatment[1]

PERFECT-RA Study



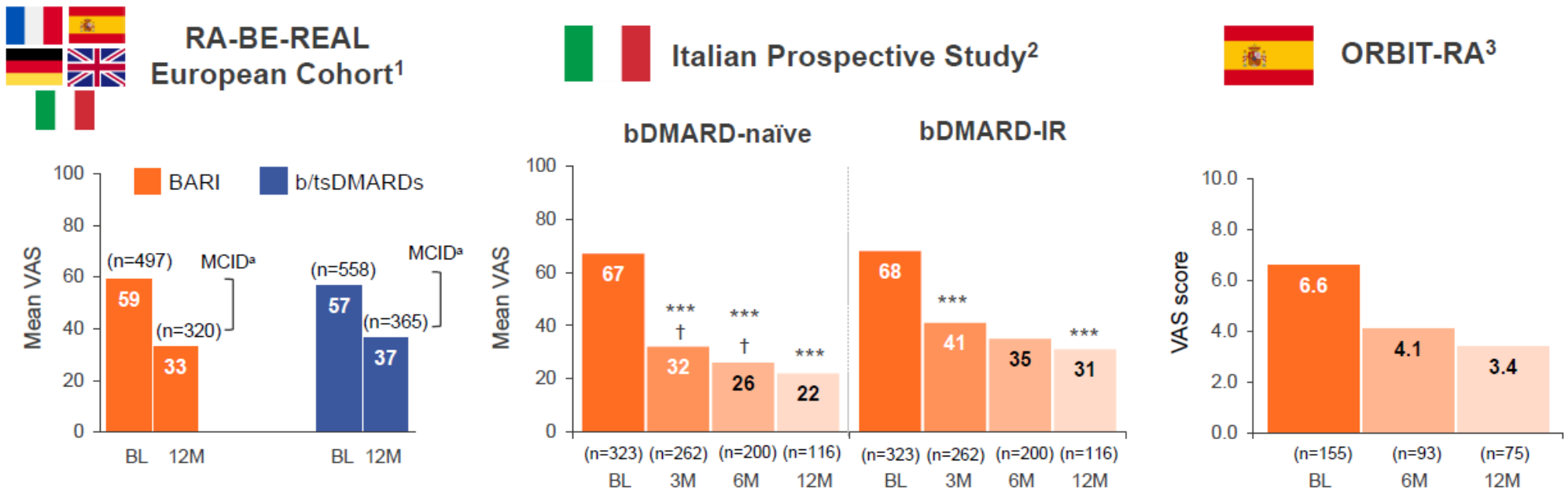
Figures show estimated marginal means. Error bars represent 95% Wald confidence interval.

BARI=Baricitinib; RAPID3-HAQ=Routine Assessment of Patient Index Data 3-Health Assessment Questionnaire; TNFi=Tumor Necrosis Factor Inhibitor; VAS=Visual Analog Scale.

1. van de Laar CJ, et al. RMD Open. 2024;10(2):e004291 (incl. Suppl.).

Baricitinib Was Associated with Pain Relief in the Real-World Setting

- Baricitinib treatment was associated with MCIDs in pain measured on the pain VAS at 12 months across multiple studies[1–3]
- In the Italian prospective study, most patients had a **significant reduction** in pain VAS as early as 3 months[2]
- In ORBIT-RA, **sustained reductions** in pain were seen at 6 and 12 months[3]



***p<0.0001 vs. baseline; †p<0.01 naive vs. IR. [a]MCID for pain VAS on a scale of 0–100 mm is 20 mm when assessing pain across the severity spectrum.[4,5]

BARI=Baricitinib; BL=Baseline; b/tsDMARD=Biologic or Targeted Synthetic Disease-Modifying Anti-Rheumatic Drug; IR=Inadequate Responder; M=Month; MCID=Minimal Clinically Important Difference; n=Number of Patients Within Specified Category; VAS=Visual Analog Scale.

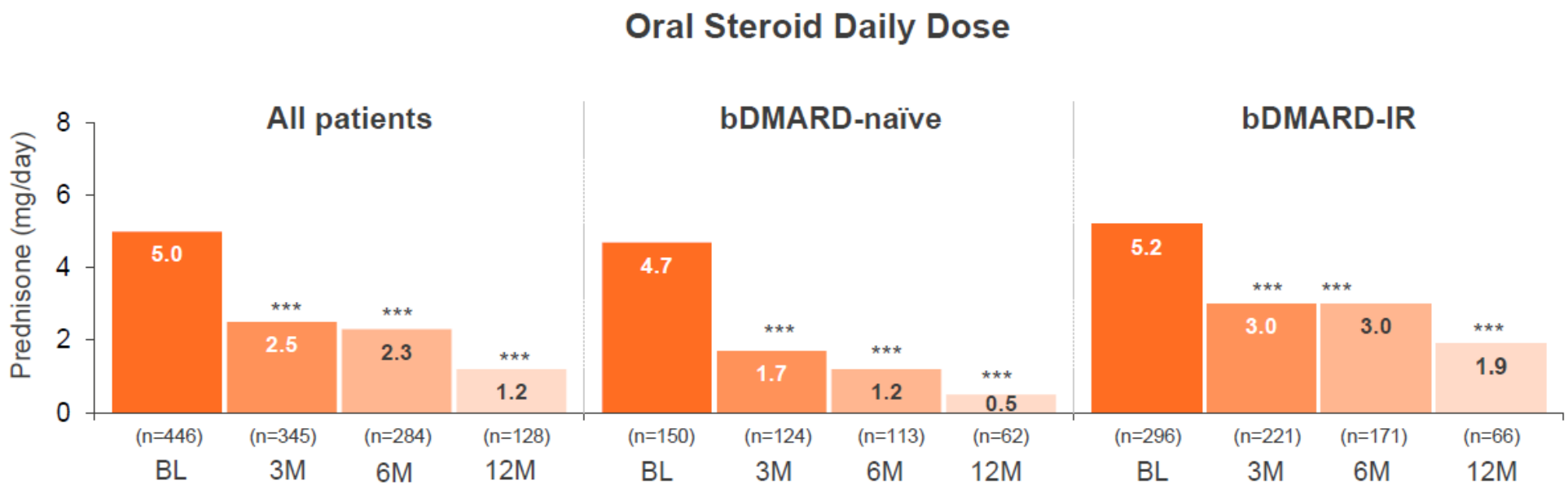
1. Alten R, et al. Poster presentation POS0666 at the European Alliance of Associations for Rheumatology (EULAR) meeting, 1– 4 June, 2022, Copenhagen, Denmark.
2. Guidelli GM, et al. Clin Exp Rheumatol. 2021;39(4):868–73. 3 Hernández-Cruz B, et al. Rheumatol Ther. 2022;9(2):589–608. 4. Dworkin RH, et al. J Pain. 2008;9(2):105–21. 5. Salaffi F, et al. Eur J Pain. 2004;8(4):283–91.

Baricitinib Was Associated with a Reduction in Steroid Use in a Real-World Setting[1]

Italian Prospective Study

Treatment Response

- A significant reduction in oral steroid dose was observed as early as 3 months in patients receiving baricitinib, regardless of prior bDMARD experience, and with or without concomitant MTX



***p<0.0001 vs. baseline.

bDMARD=Biologic Disease-Modifying Anti-Rheumatic Drug; BL=Baseline; IR=Inadequate Responder; M=Month; MTX=Methotrexate; n=Number of Patients in the Specified Category.

1. Guidelli GM, et al. Clin Exp Rheumatol. 2021;39(4):868–73.

- Efficacy across all relevant populations in RCTs
- Statistically superior in comparison to anti-TNF-a
- Rapid decline of disease activity indices
- Significant improvements in PROs
- Reduction of steroid use in RWS

Clinical case

- 65 years old female , seven -year history of seropositive erosive , RF(+), CCP (-) RA
- Comorbidities : past smoking history, A.H, Dyslipidemia BMI=32 Kg/m²
- Previous bDMARDs : Adalimumab , Tocilizumab =secondary failures
- Current treatment : Methotrexate 20 mg/week + Abatacept 125 mg/week
- D2TRA still on HDA
- ESR=42, CRP=2<0.5 ,TJC=10, SJC=4, VAS=70
- DAS-28(ESR)=5.93, CDAI=27, HAQ-DI= 1.13

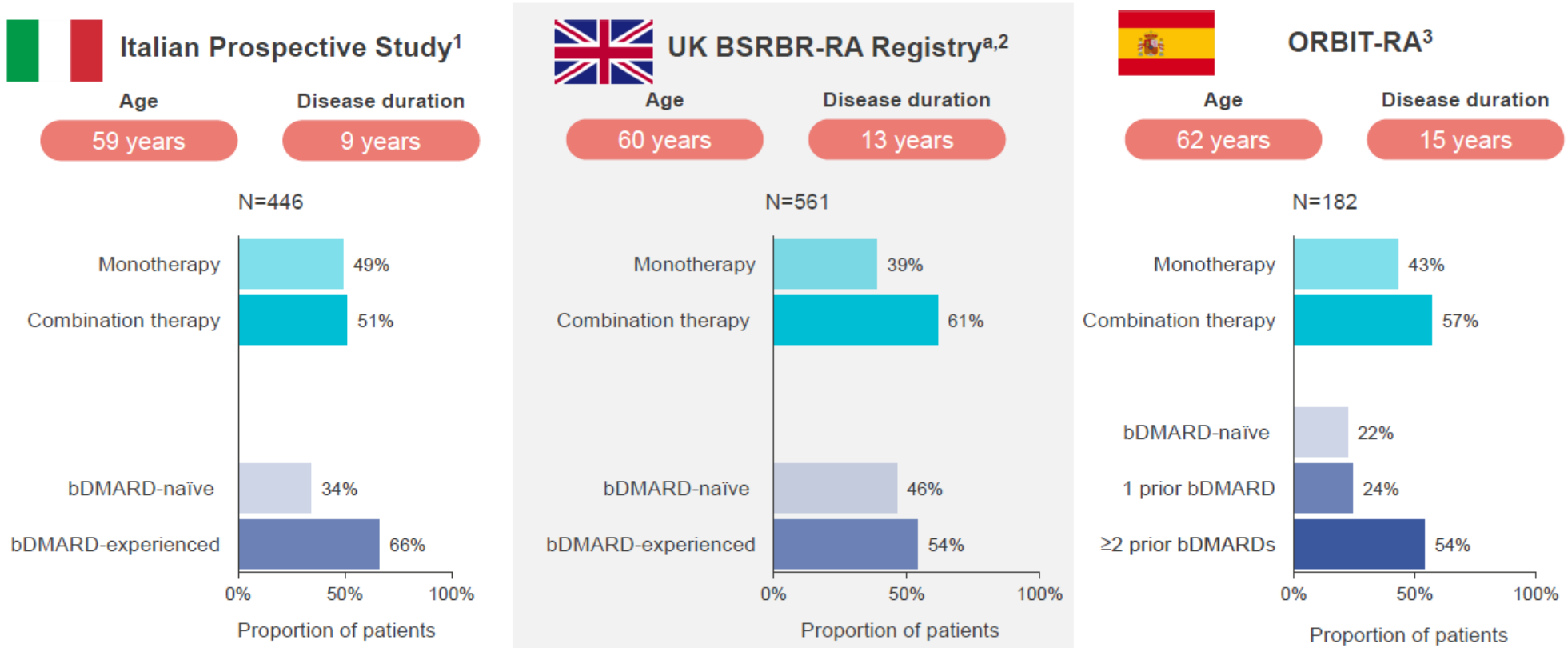
Clinical case

- Switch from ABT to Baricitinib 4 mg /day
- Four months after BARI initiation:
- ESR=18, CRP=0.8<0.5 ,TJC=2, SJC=2, VAS=30
- DAS-28(ESR)= 3.63, CDAI=10, HAQ-DI= 0.5

- Change in DAS28(ESR)=2.3> 1.2
- CDAI=LDA, index change 17
- MID :12 (if starting on HDA)

- Change in HAQ: 0.63
- MCID:0.25

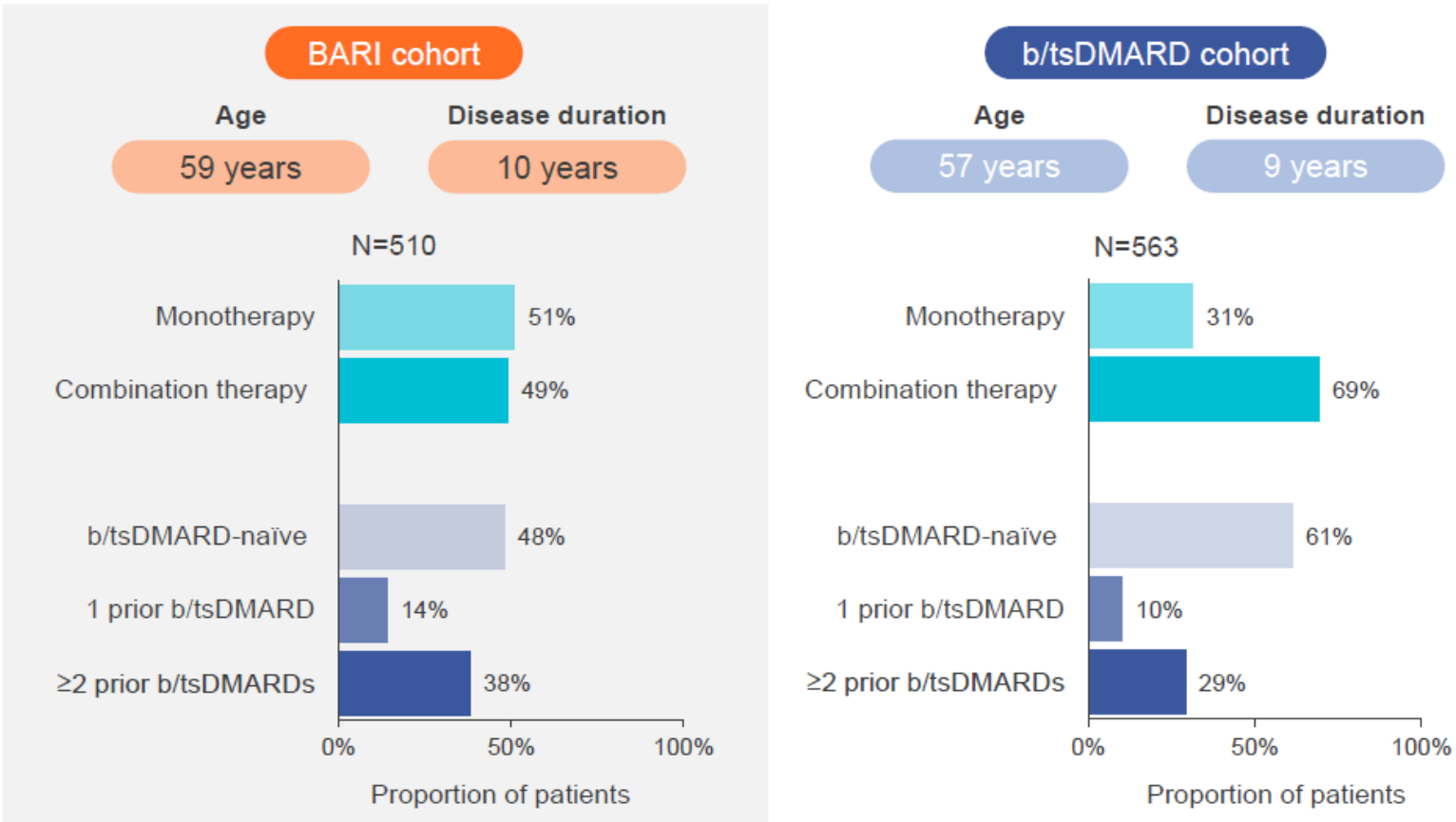
In Selected RWE Studies of Baricitinib, Most Patients Were Biologic-Experienced at Baseline



Age and disease duration values are presented as mean averages unless otherwise indicated.
bDMARD=Biologic Disease-Modifying Anti-Rheumatic Drug; BSRBR=British Society for Rheumatology Biologics Register; N=Number of Patients in the Analysis Population; RA=Rheumatoid Arthritis; RWE=Real-World Evidence.
1. Guidelli GM, et al. Clin Exp Rheumatol. 2021;39(4):868–73. 2. Edwards CJ, et al. Rheumatology (Oxford). 2023;62:3400–8. 3. Hernández-Cruz B, et al. Rheumatol Ther. 2022;9(2):589–608.

Baricitinib-Treated Patients in RA-BE-REAL Were Older and Had a Longer Duration of RA at Baseline vs. b/tsDMARD-Treated Cohorts[1]

RA-BE-REAL European Cohort



Age and disease duration values are presented as mean averages.

BARI=Baricitinib; b/tsDMARD=Biologic or Targeted Synthetic Disease-Modifying Anti-Rheumatic Drug; N=Number of Patients in the Analysis Population; RA=Rheumatoid Arthritis.

1. Alten R, et al. Rheumatol Ther. 2023;10:1575–95.

A Numerically Higher Proportion of Patients Achieved Remission with Baricitinib vs. b/tsDMARDs

RA-BE-REAL Study

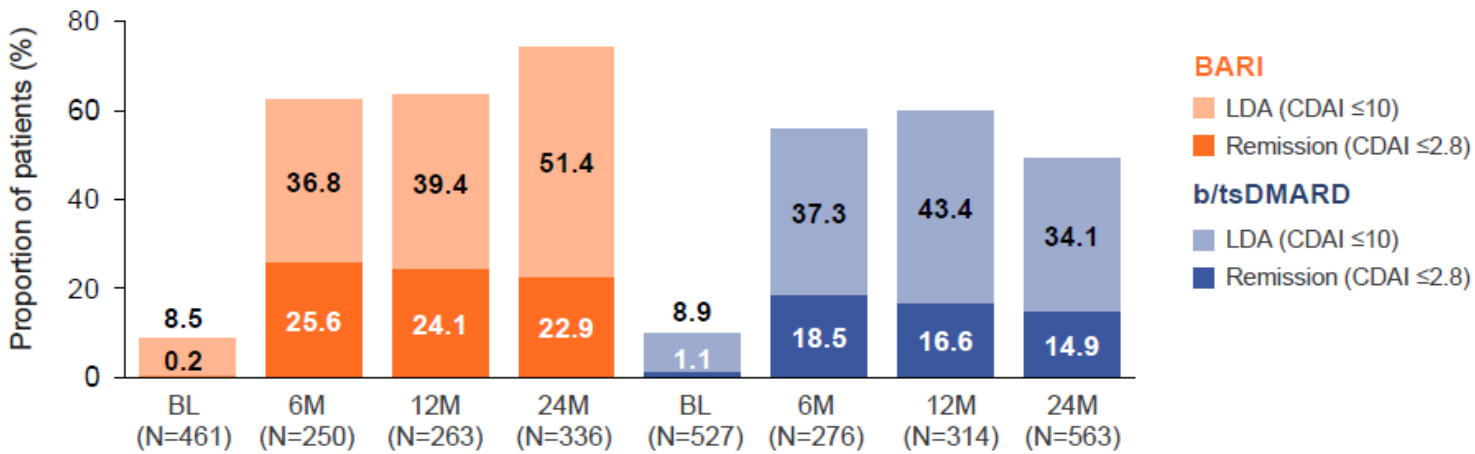
Treatment Response[1]

- Despite being older and having longer disease duration at baseline, a numerically higher percentage of patients treated with baricitinib achieved remission compared with b/tsDMARD-treated patients

Baseline characteristics[1]

	BARI	b/tsDMARD
Age, years	59	57
Disease duration, years	10	9
b/tsDMARD-naïve	48%	61%

CDAI Response Rates at 6, 12, and 24 Months[1–3]



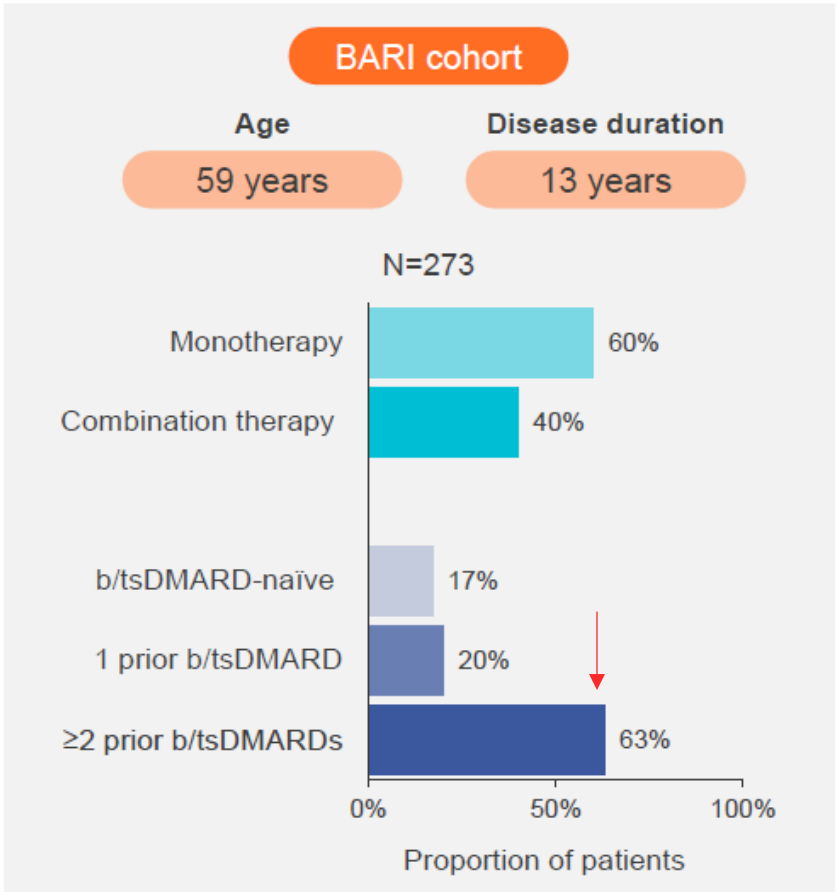
Missing values were imputed using non-responder imputation for binary variables LDA and remission. Missing values were imputed using modified Baseline Observation Carried Forward for continuous variable of CDAI.

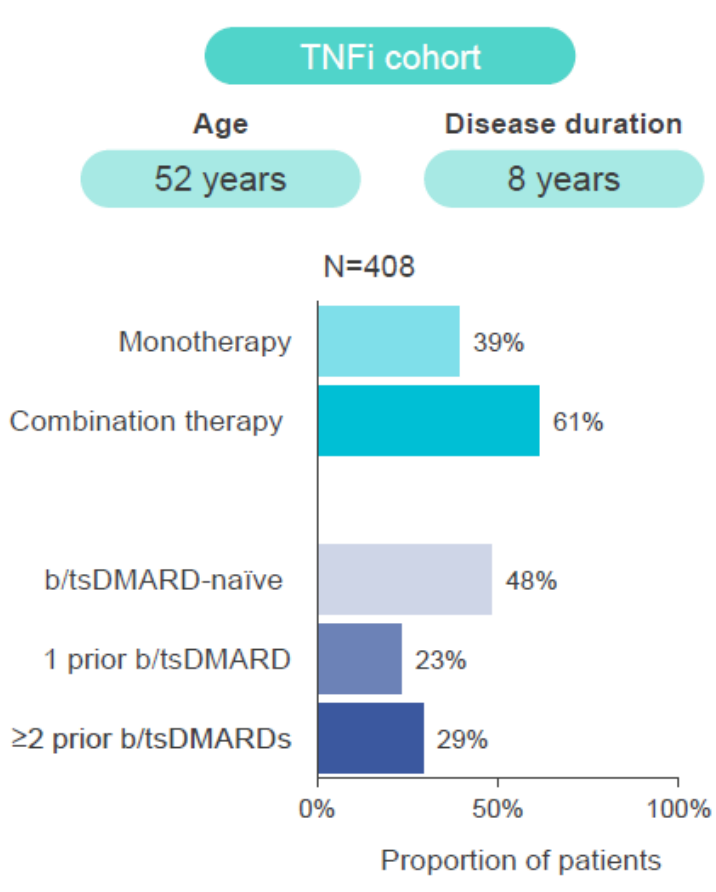
BARI=Baricitinib; BL=Baseline; b/tsDMARD=Biologic or Targeted Synthetic DMARD; CDAI=Clinical Disease Activity Index; DMARD=Disease-Modifying Anti-Rheumatic Drug; LDA=Low Disease Activity; M=Month; N=Number of Patients in the Analysis Population.

1. Alten R, et al. Rheumatol Ther. 2023;10:1575–95. 2. Alten R, et al. Rheumatol Ther. 2023;10:73–93.
3. Alten R, et al. Poster presentation POS0666 at the American College of Rheumatology (ACR) Convergence, Nov 10–14, 2022, Philadelphia, PY, USA.

In Selected RWE Studies, Baricitinib-Treated Cohorts Were Older, Had Longer Disease Duration, and Higher bDMARD Exposure vs. TNFi-Treated Cohorts[1]

Swiss SCQM-RA Cohort





Age and disease duration values are presented as mean averages unless otherwise indicated.
BARI=Baricitinib; b/tsDMARD=Biologic or Targeted Synthetic Disease-Modifying Anti-Rheumatic Drug; N=Number of Patients in the Analysis Population; RA=Rheumatoid Arthritis; RWE=Real-World Evidence; SCQM-RA=Swiss Clinical Quality Management in Rheumatoid Arthritis; TNFi=Tumor Necrosis Factor Inhibitor.

1. Gilbert BTP, et al. BMJ Open. 2024;14:e072300.

Similar Responses Achieved with Baricitinib Despite Use in Harder-to-Treat Patients vs. bDMARD-Treated Cohorts[1]

SCQM-RA Cohort

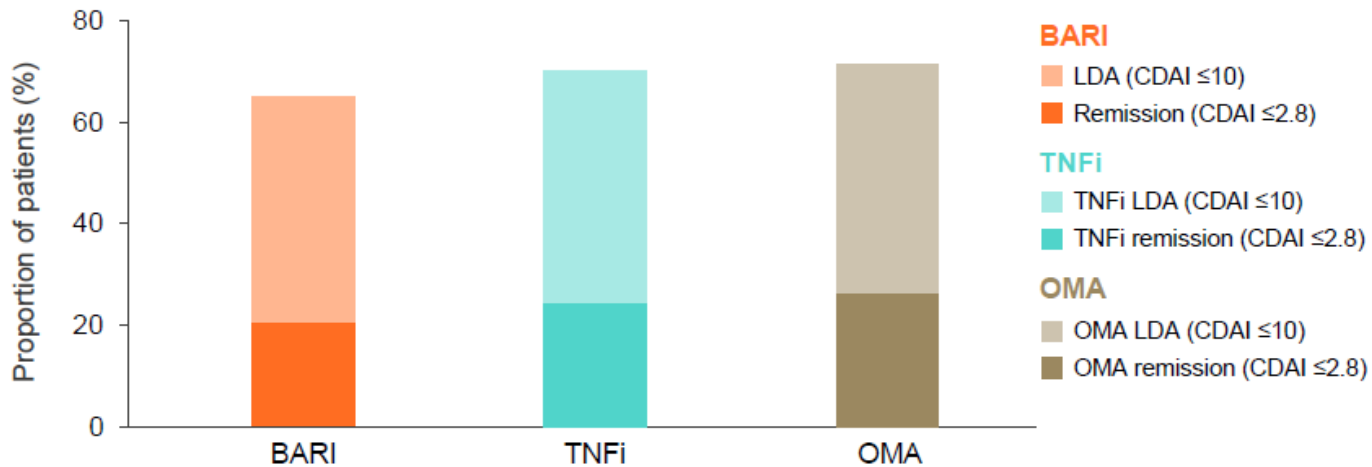
Treatment Response

- Baricitinib treatment was associated with similar LDA/remission rates despite being prescribed to older patients, with longer disease duration, and more previous treatment failures compared with the OMA and TNFi group

Baseline characteristics

	BARI (N=273)	TNFi (N=408)	OMA (N=289)
Age, years	59	52	59
Disease duration, years	13	8	11
≥4 lines of therapy	44%	18%	31%

CDAI Response Rates at 12 Months[a]



[a]Response rates computed using the CARRAC method.

BARI=Baricitinib; bDMARD=Biologic Disease-Modifying Anti-Rheumatic Drug; CARRAC= Confounder-Adjusted Response Rate with Attrition Correction; CDAI=Clinical Disease Activity Index; LDA=Low Disease Activity; N=Number of Patients in the Analysis Population; OMA=Other Mode of Action; SCQM-RA=Swiss Clinical Quality Management in Rheumatoid Arthritis; TNFi=Tumor Necrosis Factor Inhibitor.

1. Gilbert BTP, et al. BMJ Open. 2024;14:e072300.

In RWS

- **Patients treated with Baricitinib were older with longer disease duration & higher bDMARD exposure**
- **Baricitinib has shown its efficacy in harder to treat patients**
- **Similar or even numerically higher proportions of patients achieved remission in comparison with other b/ts DMARDs**

Clinical case

- 45 years old male , four years history of non-erosive seronegative RA
- Comorbidities : non smoker, A.H
- On methotrexate 15 mg/week & BARI 4 mg/day on long term clinical remission , DAS 28 ESR< 2.6 , CDAI< 2.8 on repeated clinical assessments
- Two years since diagnosis and after discussion with patient methotrexate was stopped and 6 months later patient was still on remission

Clinical case

- Further de-escalation of his treatment with reduction of BARI dose to 2 mg day according to patient preference

- Now already on BARI 2mg/day for one and a half year and patient is still on clinical remission, DAS 28 ESR< 2.6 , CDAI< 2.8 on three consecutive clinical assessments

EULAR recommends tapering DMARDs after glucocorticoids

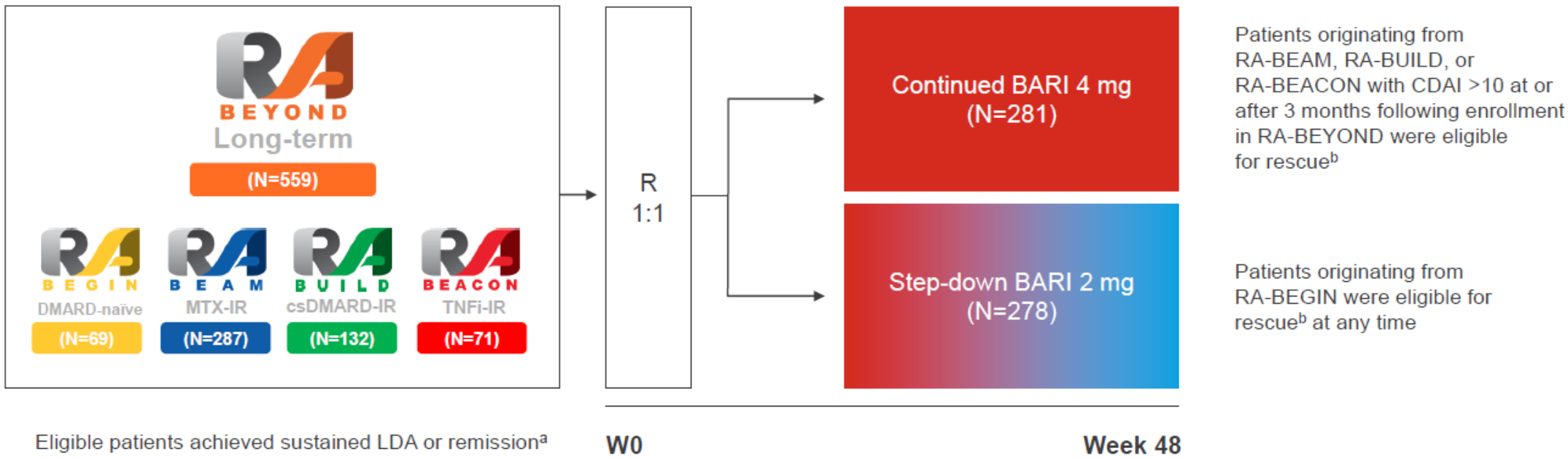
EULAR recommendations on dose tapering[a]

- If a patient is in persistent remission after having tapered glucocorticoids, one can consider **tapering bDMARDs or tsDMARDs**, especially if this treatment is combined with a csDMARD
- If a patient is in persistent remission, **tapering the csDMARD** could be considered

[a]Defined by EULAR as the reduction of drug dose or an increase of application interval. May include cessation (tapering to 0), but then only after slow reduction.
bDMARD=Biologic Disease-Modifying Antirheumatic Drug; csDMARD=Conventional Synthetic Disease-Modifying Antirheumatic Drug; EULAR=European League Against Rheumatism; tsDMARD=Targeted Synthetic Disease-Modifying Antirheumatic Drug.
Smolen JS, et al. *Ann Rheum Dis*. 2023;82:3-18.

RA-BEYOND study design: dose reduction in patients with sustained disease control

Data cut-off: September 2016

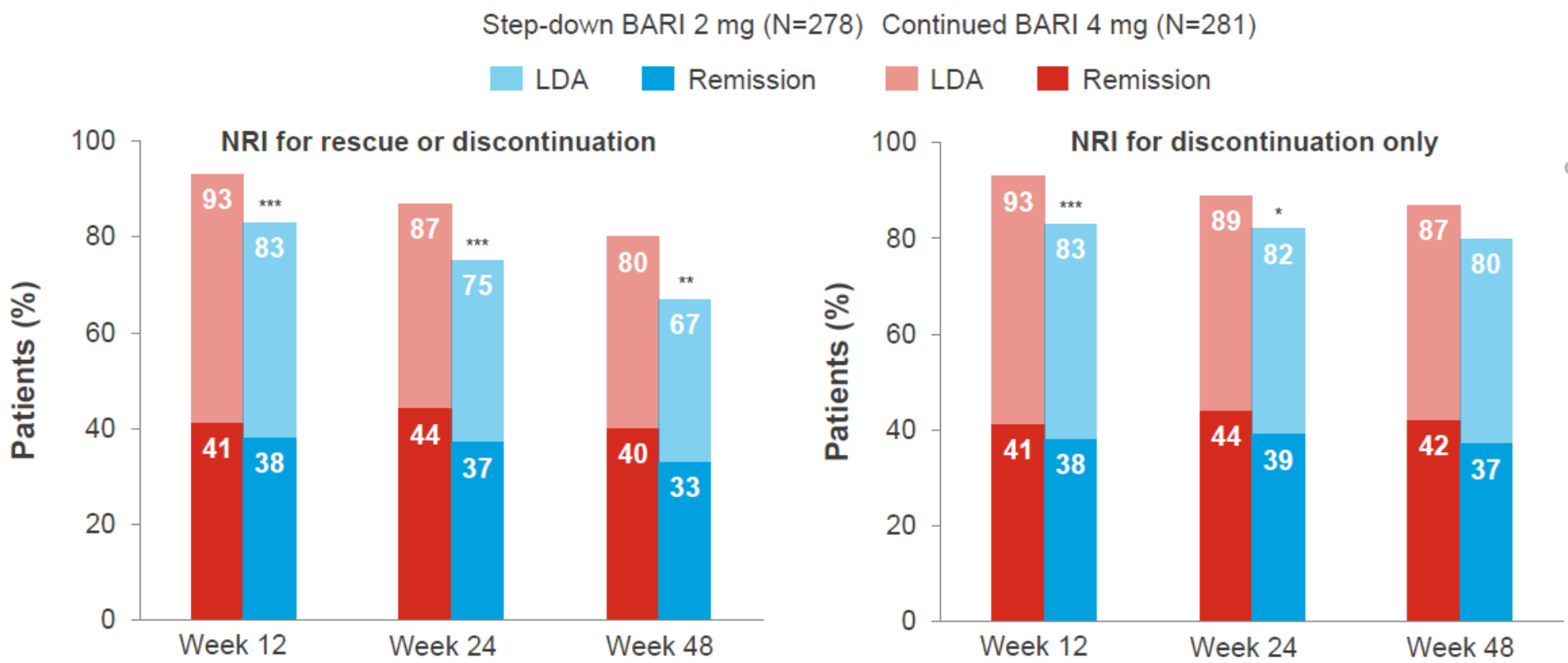


[a]Sustained LDA/remission was defined by CDAI ≤10 for patients from RA-BEAM, RA-BUILD, RA-BEACON/CDAI ≤2.8 for patients from RA-BEGIN at two consecutive visits ≥3 months apart.
[b]Rescue therapy was open-label baricitinib 4 mg and/or addition or increase of background csDMARD.
BARI=Baricitinib; CDAI=Clinical Disease Activity Index; csDMARD=Conventional Synthetic Disease-Modifying Antirheumatic Drug; IR=Inadequate Responder; LDA=Low Disease Activity; MTX=Methotrexate; N=Number of Patients in the Analysis Population; RA=Rheumatoid Arthritis; TNF=Tumor Necrosis Factor; W=Week.
Takeuchi T, et al. *Ann Rheum Dis.* 2019;78(2):171-178.

LDA/Remission were maintained up to Week 48 after step-down

Patients requiring rescue treatment were able to regain or maintain disease control

Patients achieving LDA or clinical remission through Week 48



RA BEAM MTX-IR

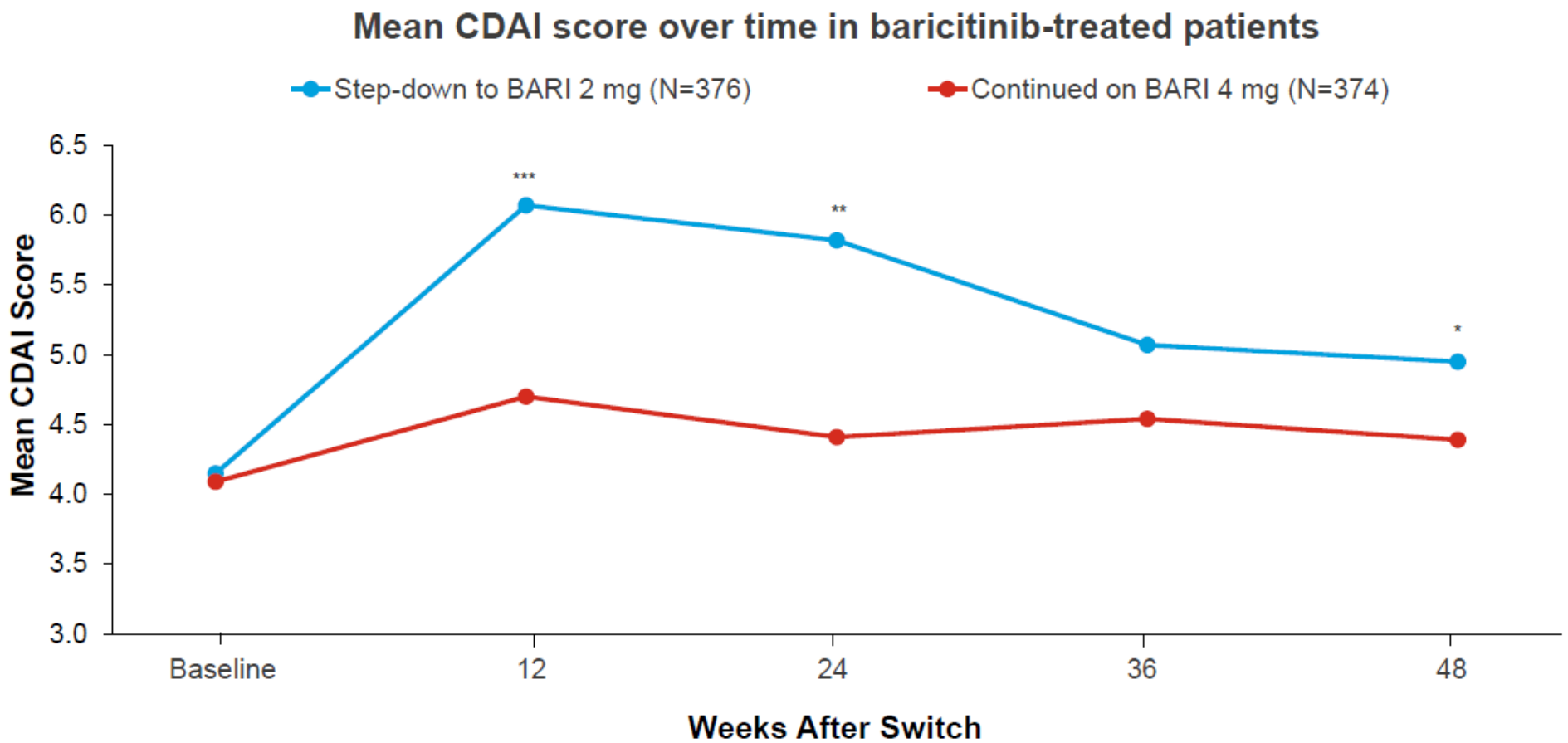
RA BUILD csDMARD-IR

RA BEACON TNFi-IR

RA BEYOND Long-term

Data cut-off: September 2016. P-value vs. continued on BARI 4 mg: ***p≤.001, **p≤.01, *p≤.05.
BARI=Baricitinib; csDMARD=Conventional Synthetic Disease-Modifying Antirheumatic Drug; IR=Inadequate Responder; LDA=Low Disease Activity; MTX=Methotrexate; N=Number of Patients in the Analysis Population; NRI=Non-responder imputation; TNFi=Tumor Necrosis Factor Inhibitor.
Takeuchi T, et al. *Ann Rheum Dis.* 2019;78(2):171-178.

Improvements in CDAI scores were maintained after step-down through Week 48



RA BEAM
MTX-IR

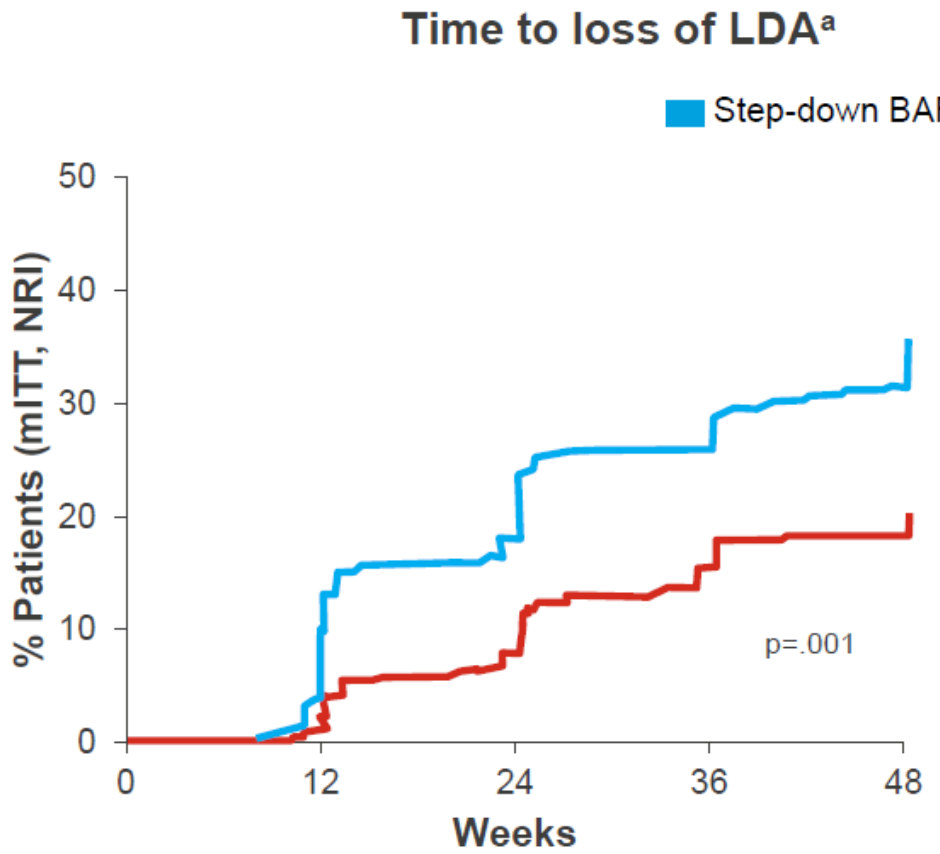
RA BUILD
csDMARD-IR

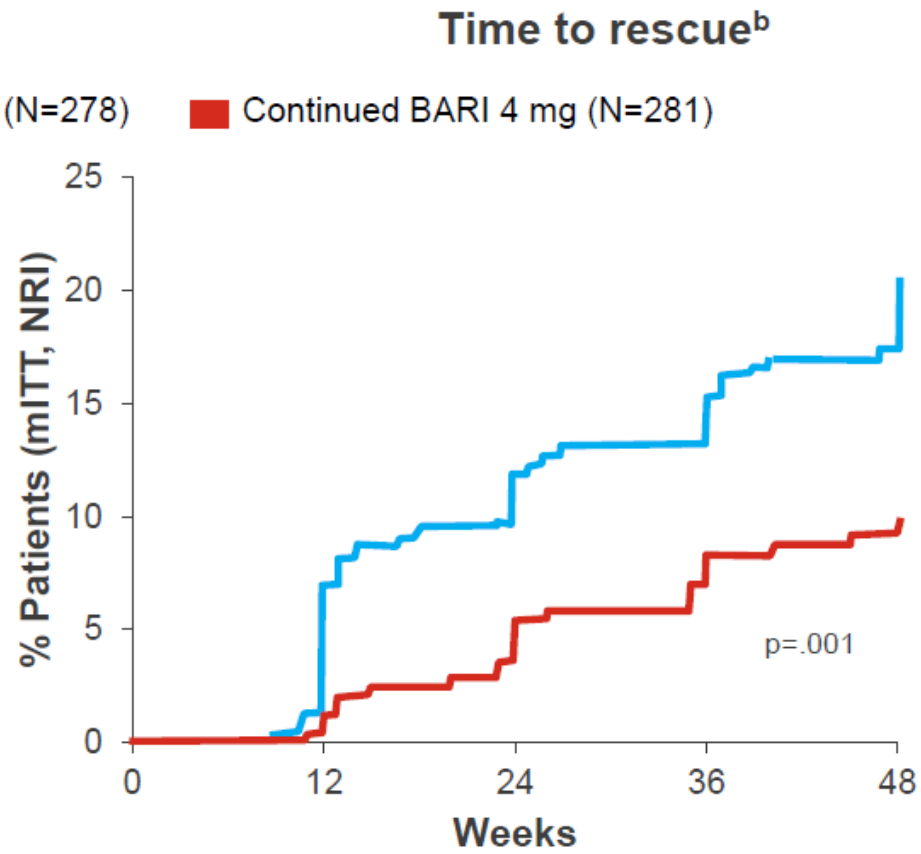
RA BEACON
TNFi-IR

RA BEYOND
Long-term

Data cut-off: September 2016. p-value vs. continued on BARI 4 mg: ***p≤.001, **p≤.01, *p≤.05.
BARI=Baricitinib; CDAI:=Clinical Disease Activity Index; csDMARD=Conventional Synthetic Disease-Modifying Antirheumatic Drug; IR=Inadequate Responder; LDA=Low Disease Activity; MTX=Methotrexate; N=Number of Patients in the Analysis Population; NRI=Non-responder imputation; TNFi=Tumor Necrosis Factor Inhibitor.
Takeuchi T, et al. *Ann Rheum Dis.* 2019;78(2):171-178.

Relapse rates for patients on baricitinib 4 mg were lower than for patients on baricitinib 2 mg at Week 48





RA BEAM MTX-IR

RA BUILD csDMARD-IR

RA BEACON TNFi-IR

RA BEYOND Long-term

vs. continued on BARI 4 mg: ***p≤.001, **p≤.01, *p≤..05

[a]Relapse was defined as loss of step-down eligibility criteria, or CDAI>10 for DMARD-IR patients originating from RA-BUILD, RA-BEAM or RA-BEACON. [b]Relapse was defined as rescue.

CDAI=Clinical Disease Activity Index; LDA=Low Disease Activity; mITT=Modified Intention To Treat Population; N=Number of Patients in the Analysis Population; NRI=Non-responder Imputation.

Takeuchi T et al. *Ann Rheum Dis*. 2019;78(2):171-178.

- **Dose flexibility**
- **Retention of remission/LDA after dose reduction in the majority of patients**

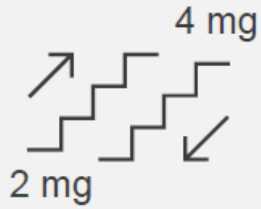
Maintenance of efficacy and flexibility are core clinical attributes of baricitinib

Maintenance of efficacy

- Long-term maintenance of LDA, remission, and normalized physical function[a,1]
- Reduced structural progression[2]
- Low discontinuation rates[3-6]

Monotherapy and combination option

- Can be used with or without MTX or other csDMARDs[7,8]



Dose options

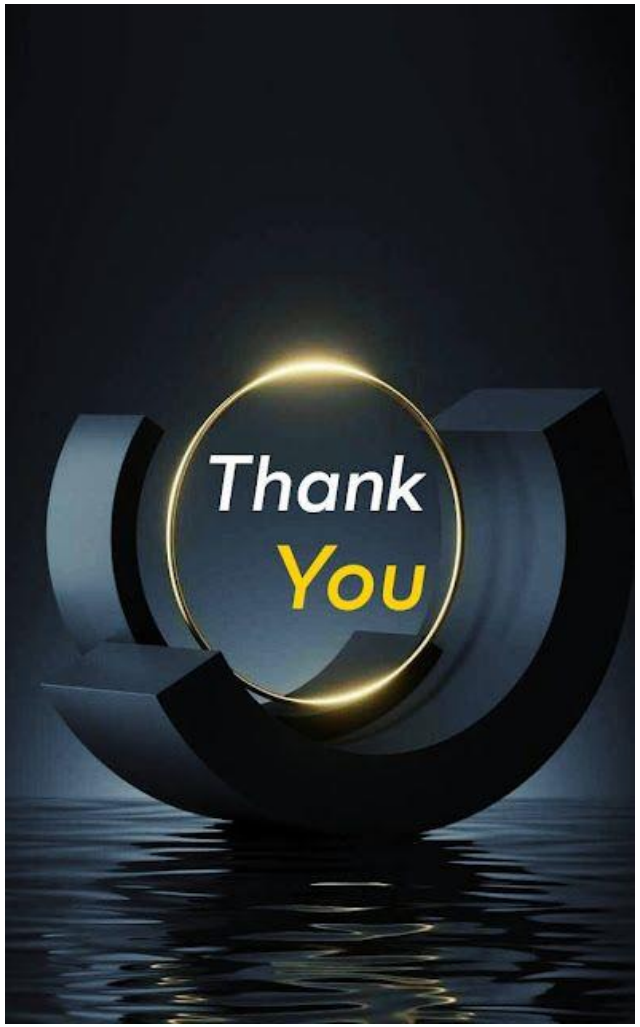
- Step-down with controlled disease[9]
- Step-up for helping to achieve treatment targets[9]
- Effective 2 mg option available if appropriate (older age, infection risk)[7,8]

Treatment interruptions

- No significant disease reactivation following brief treatment interruption[b,10]

[a]Results from 3 years of treatment with BARI 4 mg from RA-BEGIN/RA-BEAM and RA-BEYOND; [b]Interruptions in the Phase 3 program infrequent and generally of short duration (≤2 weeks).
ADA=Adalimumab; BARI=Baricitinib; csDMARD=Conventional Synthetic Disease-Modifying Antirheumatic Drug; LDA=Low Disease Activity; MTX=Methotrexate.

1. Smolen JS, et al. *Rheumatology*. 2021;60(5):2256-2266. 2. Lopez-Romero P, et al. *Ann Rheum Dis*. 2022;81(5):622-631. 3. Alten R, et al. *RMD Open*. 2022;(Communicated). 4. Gilbert B, et al. *Ann Rheum Dis*. 2021;80(Suppl 1):577-578.
5. Barbulescu A, et al. *Rheumatology*. 2022;61(10):3952-3962. 6. Egeberg A, et al. *Semin Arthritis Rheum*. 2022;53:151979. 7. Olumiant USPI. Indianapolis, IN: Lilly USA; 2018. 8. Olumiant SmPC. Utrecht: Eli Lilly Nederland B.V.; 2019.
9. Takeuchi T, et al. *Ann Rheum Dis*. 2019;78(2):171-178. 10. Emery P, et al. *Arthritis Res Ther*. 2020;22(1):115.


Thank
You

Η άποψη σας είναι πολύτιμη…

… σας ευχαριστούμε!