axPsA nuovi outcome o nuovi target?

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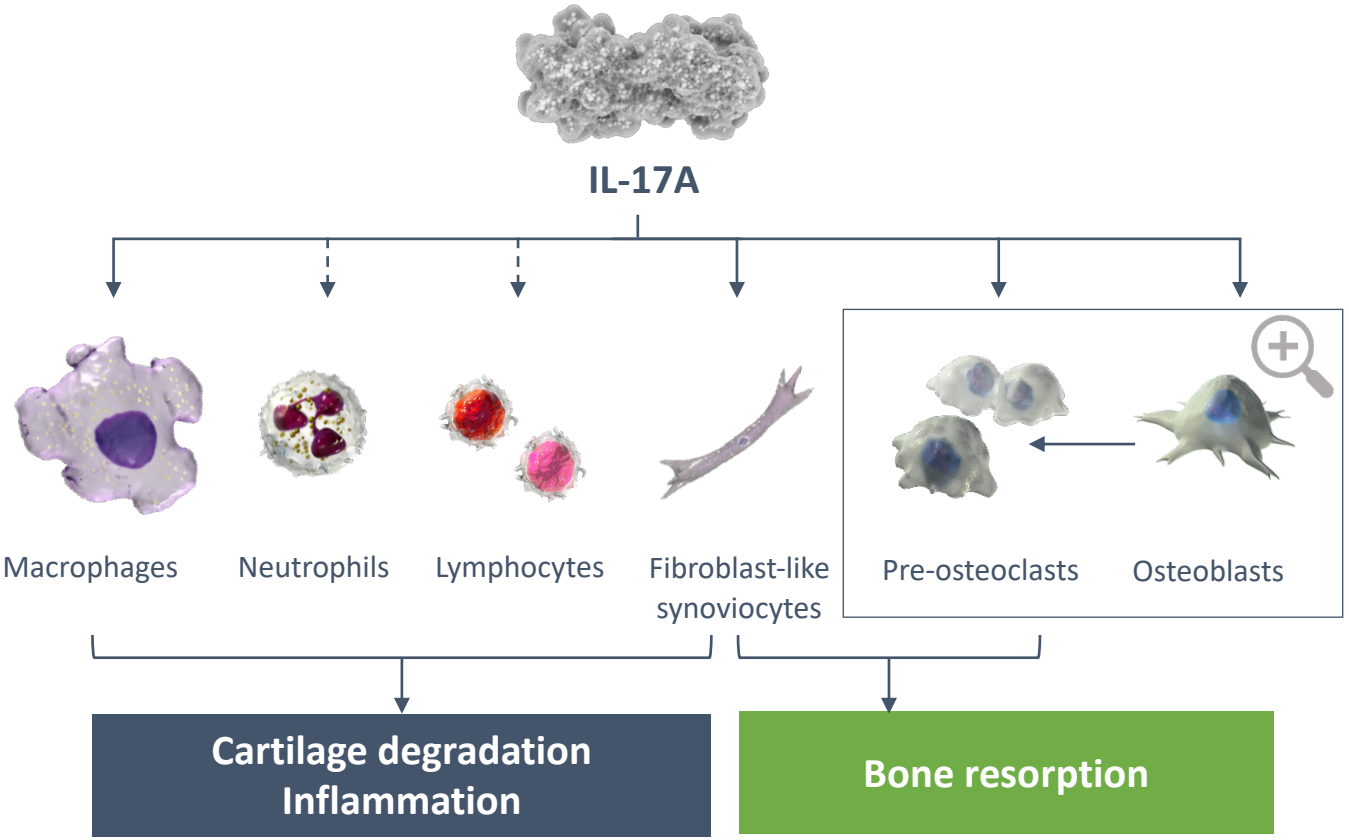
PP-IX-IT-1353 Data di deposito AIFA: 15 Sep 2021

IXEVOLUTION
un passo avanti nella gestione delle spondiloartriti

IL-17A in the Pathophysiology of axSpA

IL-17A is:

- A proinflammatory cytokine that signals through a receptor comprised of IL-17RA and IL-17RC subunits[1-3]
- Secreted by many cells of the innate and adaptive immune systems[4-10]
- Involved in the pathogenesis of synovitis, pannus formation, enthesitis, and bone degradation[11-16]
    - May also be involved indirectly in ectopic bone formation[17]



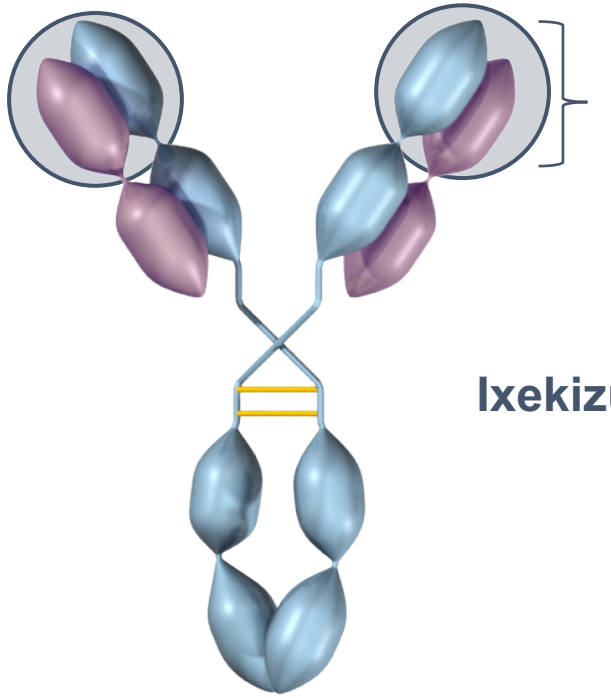
Note: MoA model is based on pre-clinical laboratory observations. Currently there are no data linking these observations to clinical efficacy or safety results. Any implications are hypotheses only.

Note: Dashed lines indicates indirect action.

1. Gaffen SL.*Nat Rev Immunol*. 2009;9:556-567. 2. Liu S, et al. *Nat Commun*. 2013;4:1888. 3. Gaffen SL, et al. *Nat Rev Immunol*. 2014;14:585-590. 4. Raychaudhuri SK, et al. *Clin Rheumatol*. 2015;34:1019-1023. 5. Schön MP. *Exp Dermatol*. 2014;23:804-806. 6. Saxena A, et al. *Arthritis Rheum*. 2011;63:1465-1466. 7. Taams LS, et al. *Nat Rev Rheumatol*. 2018;14:453-466. 8. Raychaudhuri SP, et al. *Mol Cell Biochem*. 2012;359(1-2):419-429. 9. Barin JG, et al. *Eur J Immunol*. 2012;42:726-736. 10. Dubin PJ, Kolls JK. *Immunity*. 2009;30:9-11. 11. De Vlam K, et al. *Acta Derm Venereol*. 2014;94:627-634. 12. Mease P, et al. *EMJ Rheumatol*. 2015;2:55-64. 13. Kehl AS, et al. *Arthritis Rheumatol*. 2016;68:312-322. 14. McGonagle D, et al. *Ann Rheum Dis*. 2011;70(Suppl. 1):i71-i76. 15. Sherlock JP, et al. *Nat Med*. 2012;18:1069-1076. 16. Raychaudhuri SP, Raychaudhuri SK. *Arthritis Res Ther*. 2017;19:51. 17. Osta B, et al. *Front Immunol*. 2014;5:425.

IL-17A inhibition axSpA

- Ixekizumab is an IgG4 monoclonal antibody that targets IL-17A with high binding affinity[1]
- Inhibition of IL-17A may effectively prevent joint and entheseal inflammation, cartilage and bone degradation, and possibly, ectopic bone formation[4-15]



Variable region

Ixekizumab Molecule

Half-life = 13 days[2]
Binding affinity = 1.8 pM[3]

Light chain
Heavy chain

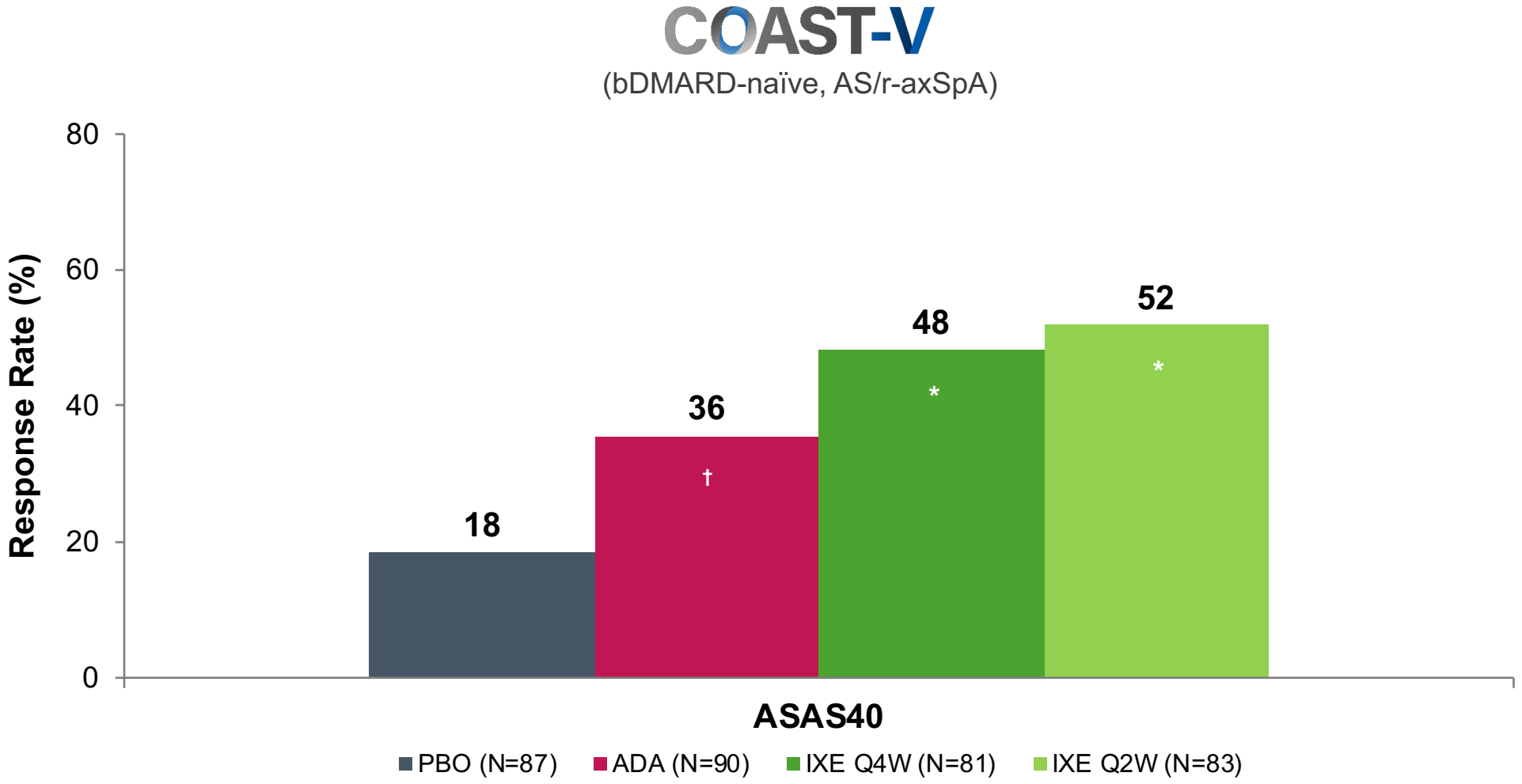
Image adapted from The Immune System. 3rd ed. Garland Science 2009.

Note: MoA model is based on pre-clinical laboratory observations. Currently there are no data linking these observations to clinical efficacy or safety results. Any implications are hypotheses only.

1. Krueger JG, et al. *J Allergy Clin Immunol*. 2012;130:145-154. 2. Taltz Riassunto delle Caratteristiche di Prodotto. 3. Liu L, et al. *J Inflamm Res*. 2016;9:39-50. 4. Raychaudhuri SK, et al. *Clin Rheumatol*. 2015;34:1019-1023. 5. Taams LS, et al. *Nat Rev Rheumatol*. 2018;14:453-466. 6. Raychaudhuri SP, et al. *Mol Cell Biochem*. 2012;359:419-429. 7. De Vlam K, et al. *Acta Derm Venereol*. 2014;94:627-634. 8. Mease P, et al. *EMJ Rheumatol*. 2015;2:55-64. 9. Kehl AS, et al. *Arthritis Rheumatol*. 2016;68:312-322. 10. Raychaudhuri SP, Raychaudhuri SK. *Arthritis Res Ther*. 2017;19:51. 11. Suzuki E, et al. *Autoimmun Rev*. 2014;13:496-502. 12. Osta B, et al. *Front Immunol*. 2014;5:48. 13. Lee Y. *BMB Rep*. 2013;46:479-483. 14. Onishi RM, Gaffen SL. *Immunology*. 2010;129:311-321. 15. Caetano-Lopes J, et al. *Autoimmun Rev*. 2009;8:250-255.

Primary Endpoint: ASAS40 Response at Week 16, NRI

Blinded Dosing Period, ITT Population



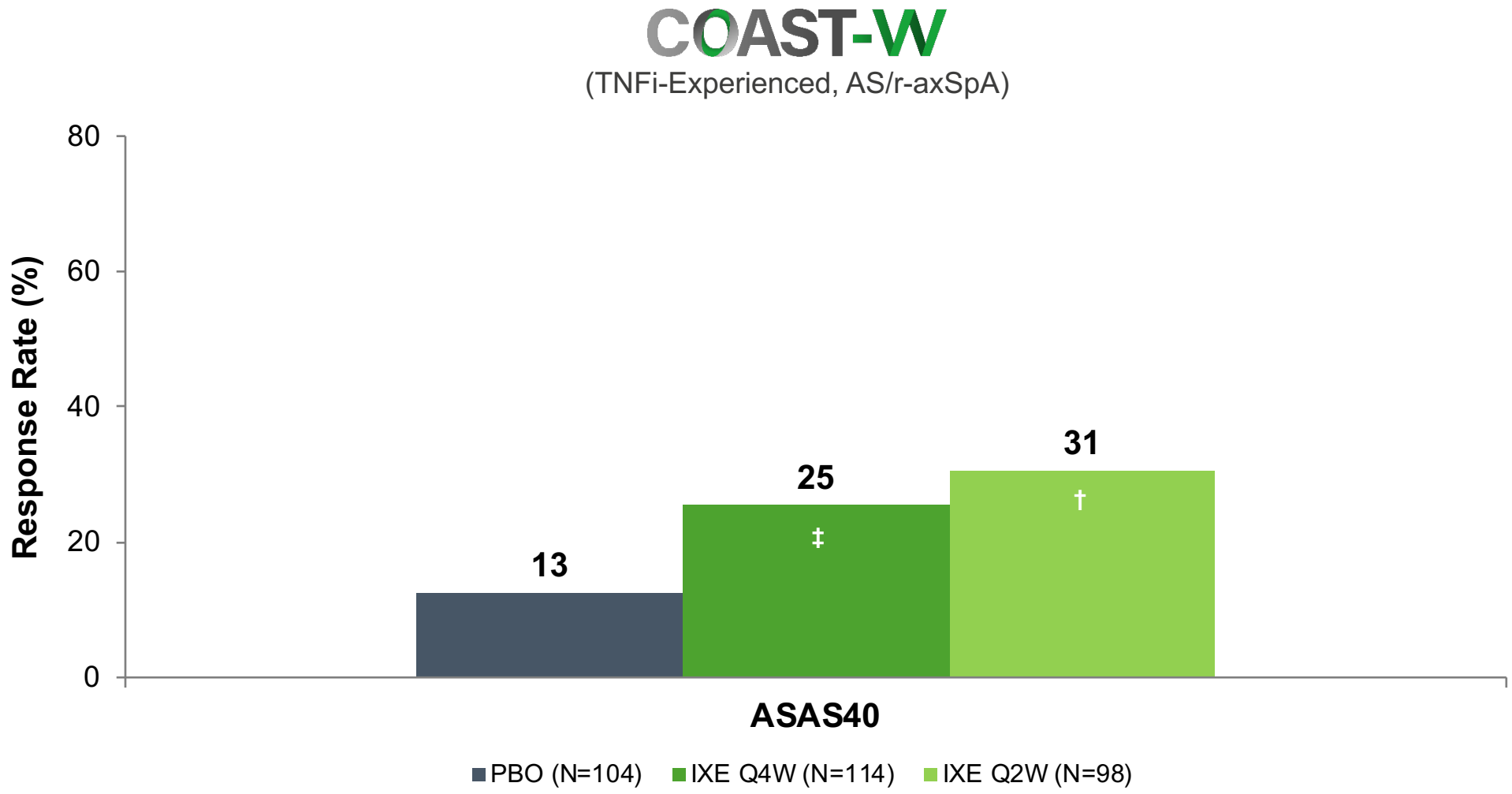
*p≤.001 vs. PBO; †p≤.01 vs. PBO.

ADA represents an active reference; the study was not powered to test equivalence or noninferiority of active treatment groups to each other, including IXE vs. ADA.

van der Heijde D, et al. *Lancet.* 2018;392:2441-2451.

Primary Endpoint: ASAS40 Response at Week 16, NRI

Blinded Dosing Period, ITT Population

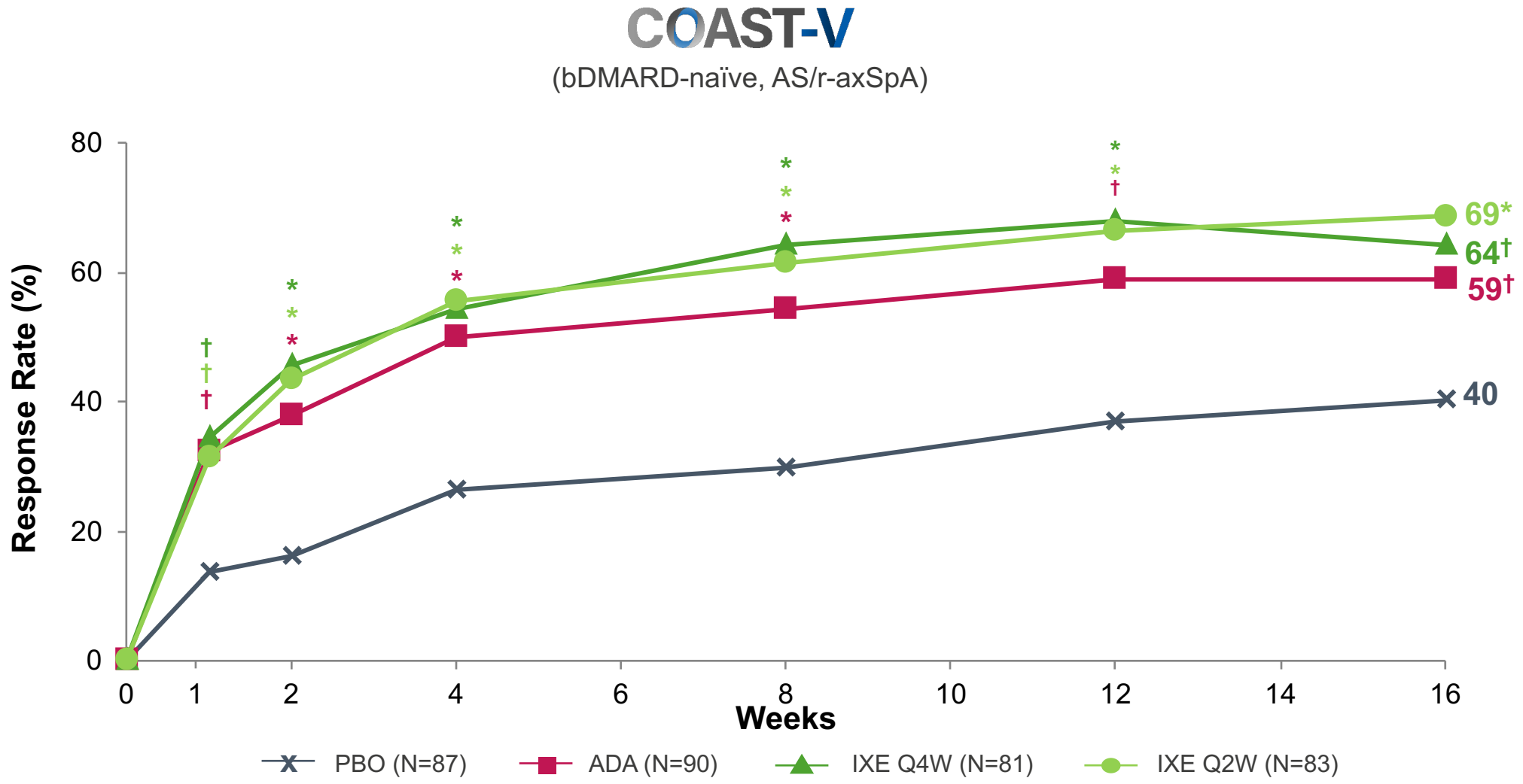


†p≤.01 vs. PBO; ‡p<.05 vs. PBO.

Deodhar A, et al. *Arthritis Rheumatol.* 2019;71:599-611.

ASAS20 Response Rates Through Week 16, NRI

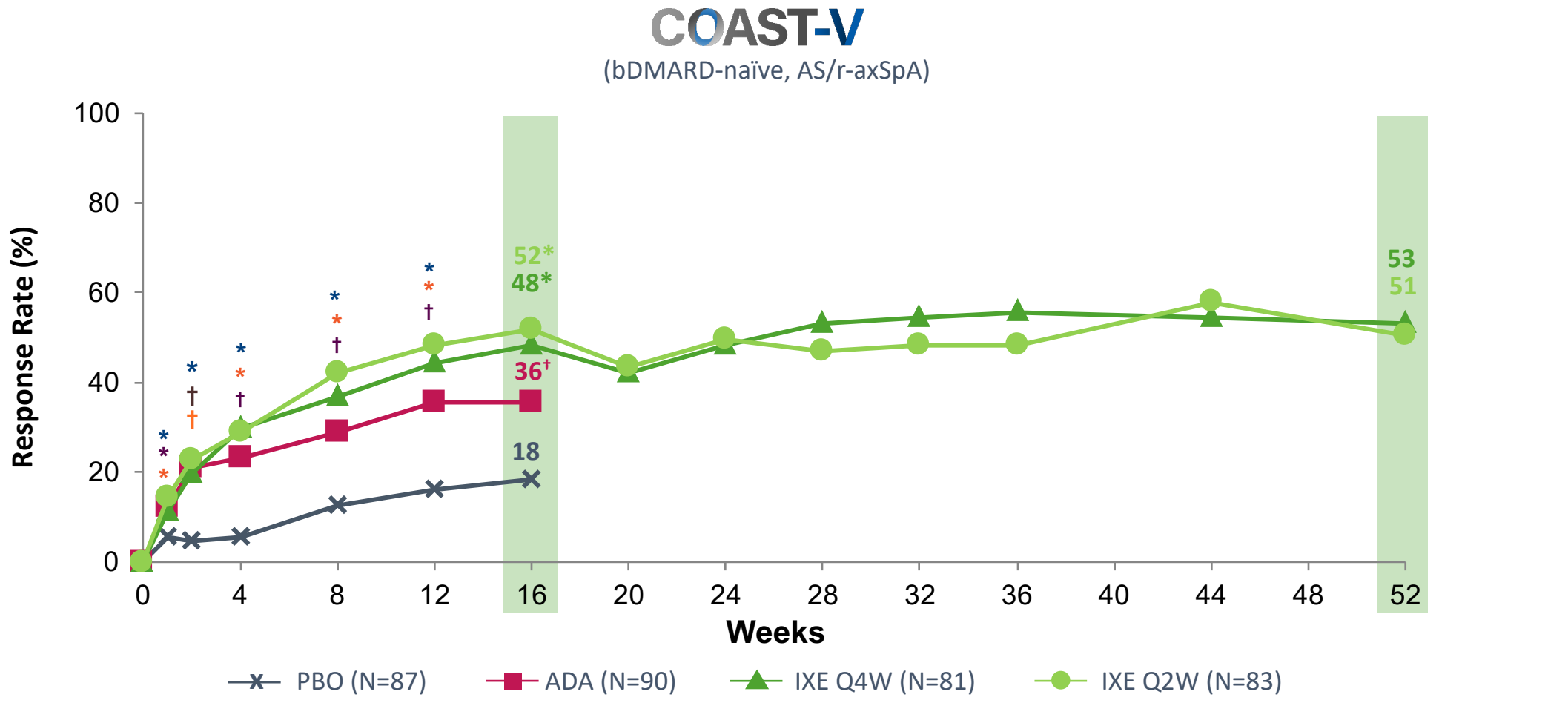
Blinded Dosing Period, ITT Population



*p≤.001 vs. PBO; †p<.01 vs. PBO.
Note: ADA represents an active reference; the study was not powered to test equivalence or noninferiority of active treatment groups to each other, including IXE vs. ADA.
van der Heijde D, et al. *Lancet.* 2018;392:2441-2451.

ASAS40 Response Rates Through Week 52, NRI[1-3]

Double-Blind PBO-Controlled and Dose Double-Blind Extended Treatment Periods, ITT Population



Statistically significant improvements in ASAS40 response rate vs. PBO were seen as early as Week 2 in COAST-V. Responses were maintained through Week 52.

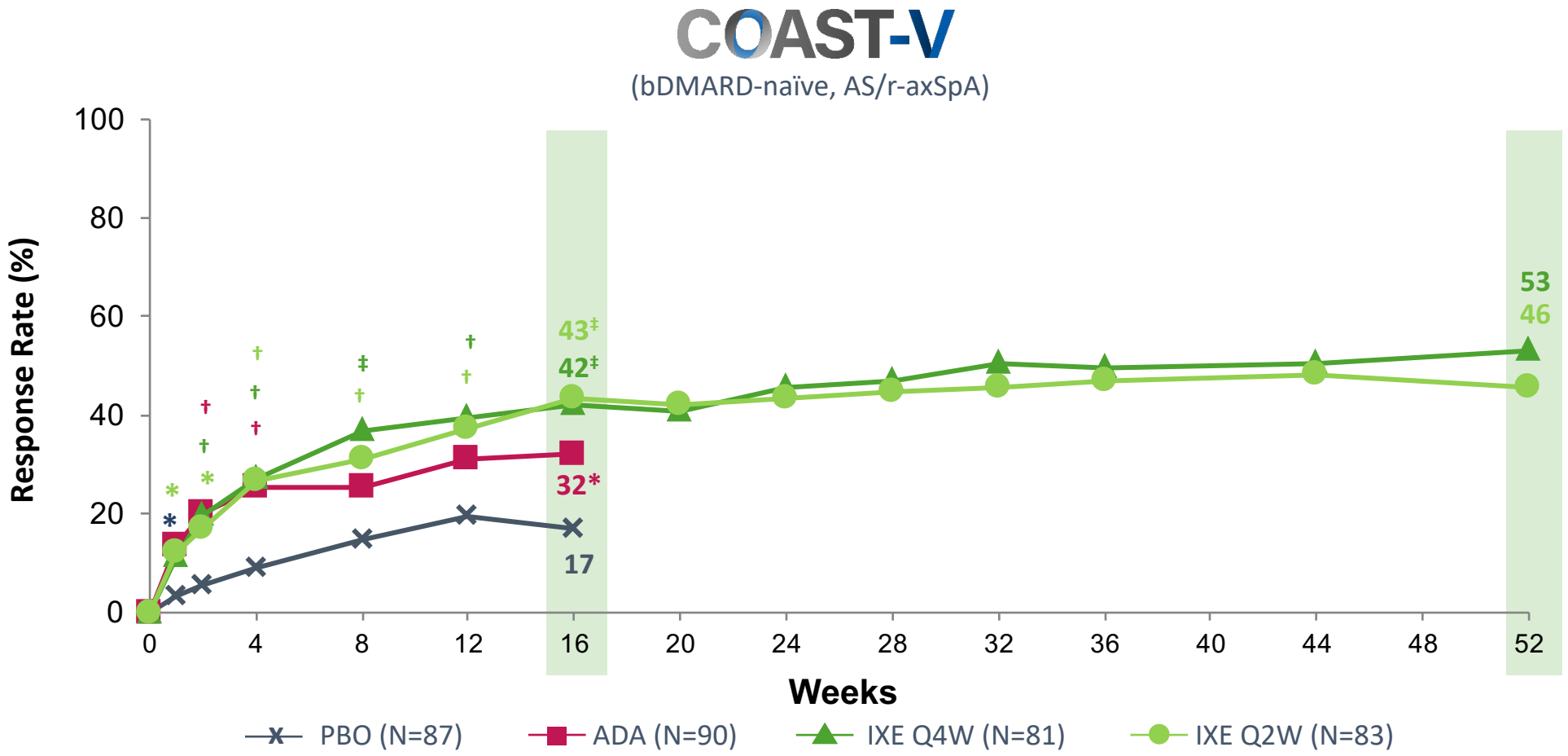
*p≤.001 vs. PBO; †p<.01 vs. PBO; ‡p<.05 vs. PBO.

Note: ADA represents an active reference; COAST-V was not powered to test equivalence or noninferiority of active treatment groups to each other, including IXE vs. ADA.

1. van der Heijde D, et al. *Lancet.* 2018;392:2441-2451. 2. Dougados M, et al. *Ann Rheum Dis.* 2020;79:176-185.

BASDAI50 Response Rate Through Week 52, NRI[1]

Double-Blind PBO-Controlled and Dose Double-Blind Extended Treatment Periods, ITT Population



The proportion of IXE-treated patients achieving BASDAI50 response rate at Week 16 was significantly higher than PBO. Responses were maintained through Week 52

*p≤.001 vs. PBO; †p≤.01 vs. PBO; ‡p<.05 vs. PBO.

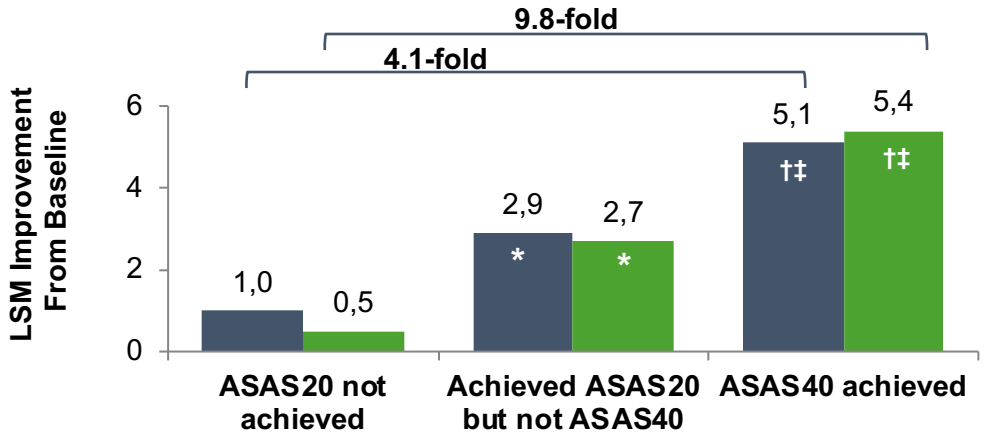
Note: ADA represents an active reference arm; the study was not powered to test equivalence or noninferiority of active treatment groups to each other, including IXE vs. ADA.

1. van der Heijde D, et al. *Lancet.* 2018;392:2441-2451.

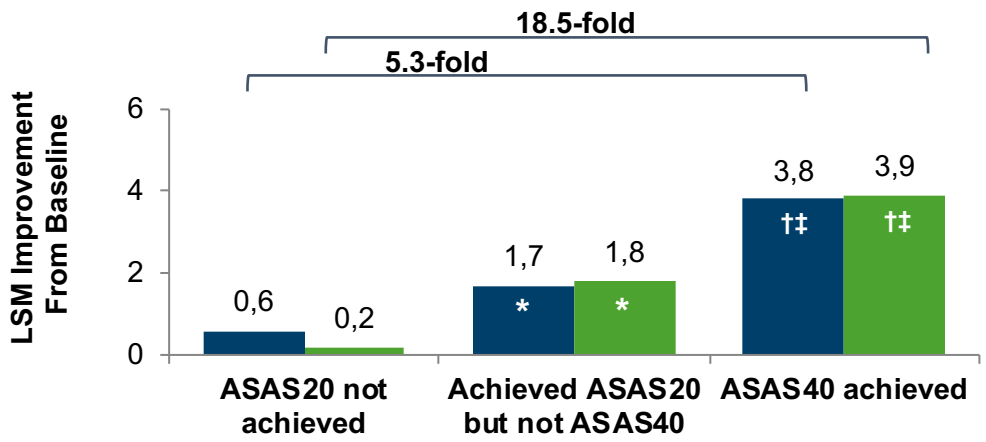
ASAS40 Response is Associated With Significantly Better Patient Reported Outcomes Thus Representing a Higher Clinical Standard

Data from COAST -V and COAST-W

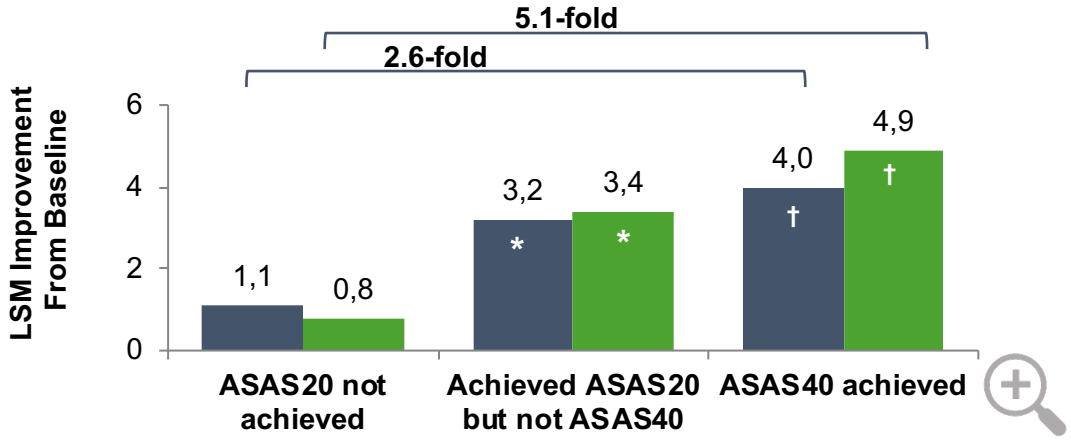
Spinal Pain at Night at Week 16, mBOCF



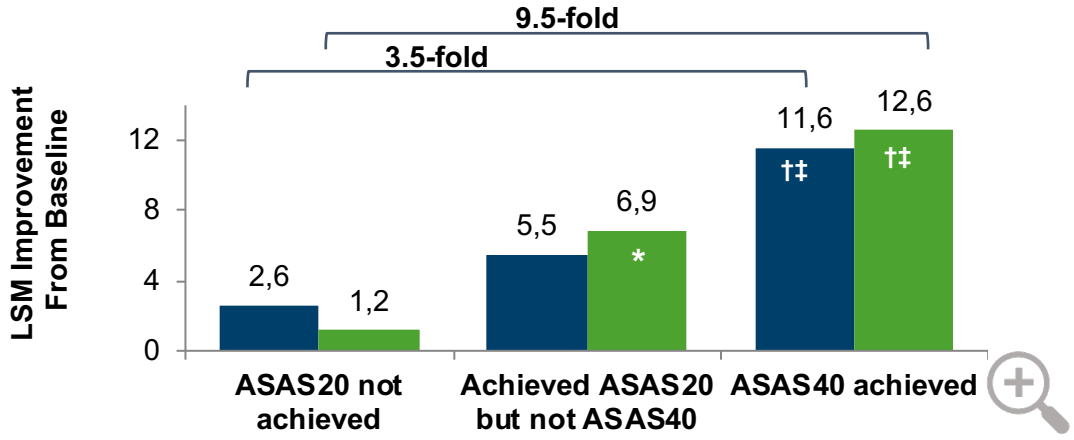
Fatigue NRS at Week 16, mBOCF



Sleep Quality (JESQ) at Week 16, mBOCF



SF-36 PCS at Week 16, mBOCF



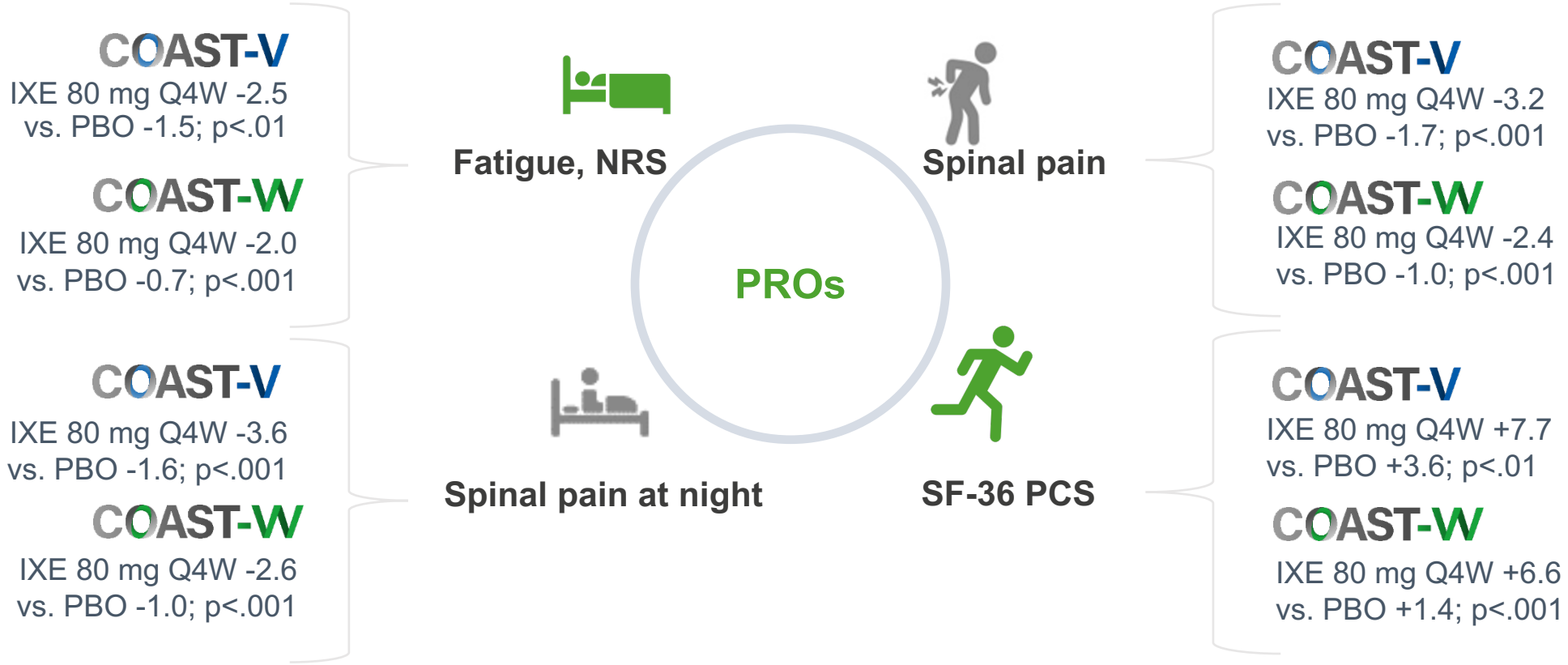
bDMARD-naïve (COAST-V) (N=341) TNFi-experienced (COAST-W) (N=316)

*p<.001 achieved ASAS20 but not ASAS40 vs. ASAS20 not achieved; †p<.0001, ASAS40 achieved vs. ASAS20 not achieved; ‡p<.0001 ASAS40 achieved vs. achieved ASAS20 but not ASAS40.

Mease P, et al. *Rheumatol Ther*. 2019;6:435-450.

Improvements in Symptoms Translates Into Significant Improvements in PROs[1,2]

COAST-V (bDMARD-naïve, AS/r-axSpA) and COAST-W (TNFi-experienced, AS/r-axSpA)



1. Mease P, et al. *Rheumatol Ther*. 2019;6:435-450. 2. Deodhar A, et al. *Arthritis Rheumatol*. 2019;71:599-611.

COAST-V

Summary of Major Efficacy Findings

Significant Endpoints at Week 16[a]	
ASAS40 response (%)	✓
ASAS20 response (%)	✓
ASDAS, mean change from baseline	✓
BASDAI50 response (%)	✓
BASFI, mean change from baseline	✓
MRI Spine, mean change from baseline	✓
ASDAS inactive disease (%)	✓
ASAS HI, mean change from baseline	✓
SF36-PCS, mean change from baseline	✓

[a]Primary and major secondary endpoints were analyzed according to a prespecified graphical multiplicity adjustment approach. [b]Primary and major secondary endpoints were also significant for Q2W.

van der Heijde D, et al. *Lancet*. 2018;392:2441-2451.

COAST-W

Summary of Major Efficacy Findings

Significant Endpoints at Week 16[a]	
ASAS40 response (%)	✓
ASAS20 response (%)	✓
ASDAS, mean change from baseline	✓
BASDAI, mean change from baseline	✓
BASFI, mean change from baseline	✓
MRI Spine, mean change from baseline	✓
ASDAS low disease activity/ inactive disease (%)	✓
ASAS HI, mean change from baseline	✓
SF36-PCS, mean change from baseline	✓

[a]Primary and major secondary endpoints were analyzed according to a prespecified graphical multiplicity adjustment approach. [b]Primary and all major secondary endpoints except ASAS HI were significant for Q2W.

Deodhar A, et al. *Arthritis Rheumatol*. 2019;71:599-611.

Safety profile

Summary of reported adverse events (IR per 100 P.Y.)

	Pazienti con PsO in trattamento con Ixekizumab (n=5898)			Pazienti con PsA in trattamento con Ixekizumab (n=1401)			Pazienti con axSpA in trattamento con Ixekizumab (n=929)		
Anni-paziente totali	17331,1			2228,6			1336,2		
Giorni di esposizione (minimo-massimo)	1-2236			8-1219			15-990		
Esposizione media (giorni/paziente)	1073,3			581,4			525,3		
Esposizione mediana (giorni/paziente)	1177,0			504,5			533,0		
	n (%)	**IR**	**95% CI**	**n (%)**	**IR**	**95% CI**	**n (%)**	**IR**	**95% CI**
Morte	35 (0,6)	0,2	0,1 - 0,3	6 (0,4)	0,3	0,1 - 0,6	2 (0,2)	0,1	0,0 - 0,6
Eventi avversi che hanno portato a interruzione (incluso il decesso)	488 (8,3)	2,8	2,6 - 3,1	114 (8,1)	5,1	4,3 - 6,1	52 (5,6)	3,9	3,0 - 5,1
Eventi avversi severi[a]	933 (15,8)	5,4	5,0 - 5,7	133 (9,5)	6,0	5,0 - 7,1	74 (8,0)	5,5	4,4 -7,0
Pazienti con ≥1 TEAE[b]	5108 (86,6)	29,5	28,7 - 30,3	1128 (80,5)	50,6	47,7 - 53,7	747 (80,4)	55,9	52,0 - 60,1
Lievi	1342 (22,8)	7,7	7,3 - 8,2	461 (32,9)	20,7	18,9 - 22,7	306 (32,9)	22,9	20,5 - 25,6
Moderati	2778 (47,1)	16,0	15,4 - 16,6	553 (39,5)	24,8	22,8 - 27,0	358 (38,5)	26,8	24,2 - 29,7
Severi	987 (16,7)	5,7	5,4 - 6,1	114 (8,1)	5,1	4,3 - 6,1	83 (8,9)	6,2	5,0 - 7,7
TEAE più comuni[c]									
Nasofaringite	1518 (25,7)	8,8	8,3 - 9,2	202 (14,4)	9,1	7,9 - 10,4	147 (15,8)	11,0	9,4 - 12,9
Infezioni del tratto respiratorio superiore	923 (15,6)	5,3	5,0 - 5,7	185 (13,2)	8,3	7,2 - 9,6	98 (10,5)	7,3	6,0 - 8,9
Reazioni nel sito di iniezione	573 (9,7)	3,3	3,0 - 3,6	156 (11,1)	7,0	6,0 - 8,2	91 (9,8)	6,8	5,5 - 8,4
Mal di testa	509 (8,6)	2,9	2,7 - 3,2	56 (4,0)	2,5	1,9 - 3,3	31 (3,3)	2,3	1,6 - 3,3

[a]La raccolta dei dati per il database degli studi clinici non contiene specifiche sul momento in cui gli eventi diventano gravi, i numeri possono rappresentare un numero maggiore di eventi considerati gravi rispetto al numero di eventi effettivamente gravi durante il periodo di trattamento,
[b]I pazienti con più occorrenze dello stesso evento vengono conteggiati sotto la gravità più elevata, IR: tasso di incidenza; N: numero di pazienti nella popolazione in analisi; n: numero di pazienti in ciascuna categoria; PsO: psoriasi; PsA: artrite psoriasica; SAE: evento avverso severo; TEAE: evento avverso emergente dal trattamento. [c]I TEAE più comuni sono definiti come IR>2,0

Genovese MC, et al. Rheumatology (Oxford). 2020; doi:10.1093/rheumatology/keaa189 (Ahead of print)

Product information

Classe H - Medicinale soggetto a prescrizione medica limitativa, vendibile al pubblico su prescrizione di centri ospedalieri o di specialisti - internista, reumatologo, dermatologo (RRL).

TALTZ 80 mg soluzione iniettabile in penna preriempita – 2 penne preriempite - AIC n° 044863025/E
Prezzo al pubblico: € 3.518,73 Prezzo ex-factory: € 2.132,00

TALTZ 80 mg soluzione iniettabile in siringa preriempita – 2 siringhe preriempite - AIC n° 044863052/E
Prezzo al pubblico: € 3.518,73 Prezzo ex-factory: € 2.132,00

Clicchi qui per RCP Taltz