A Novel Composite Endpoint Including Low Peripheral Joint Disease Activity State and Clear/Almost Clear Skin in Patients With Active Psoriatic Arthritis

Daniel Aletaha,[1] Joseph F. Merola,[2] Mohammed Sharaf,[3] Natalie J. Shiff,[4,5] Emmanouil Rampakakis,[6,7] Kate Callaway,[4*] Francois Nantel,[8] Frederic Lavie,[9] Anna Molto,[10] Alexis Ogdie[11]

[1]Department of Medicine III, Division of Rheumatology, Medical University of Vienna, Vienna, Austria; [2]Department of Dermatology, Department of Medicine, Division of Rheumatology, UT Southwestern Medical Center, Dallas, TX, USA; [3]Johnson & Johnson MEA, Dubai Healthcare City, Dubai, UAE; [4]Immunology, Johnson & Johnson, Horsham, PA, USA; [5]Adjunct, Community Health and Epidemiology, University of Saskatchewan, Saskatoon, SK, Canada; [6]JSS Medical Research, Inc, Montreal, QC, Canada; [7]Department of Pediatrics, McGill University, Montreal, QC, Canada; [8]Nantel Medsci Consult, Montreal, QC, Canada; [9]Immunology, Johnson & Johnson, Issy les Moulineaux, France; [10]Cochin Hospital, APHP, Paris, Île-de-France, France; [11]University of Pennsylvania School of Medicine, Division of Rheumatology, Philadelphia, PA, USA

Background

Psoriatic arthritis (PsA) is a multidomain disorder associated with peripheral and axial joint inflammation, enthesitis, dactylitis, and skin/nail psoriasis (PsO)

Existing tools for assessing PsA include:
- PsA Disease Activity Score (PASDAS)[1]: peripheral joints, enthesitis, dactylitis, physician global assessment (GA), physical function, and patient (pt) GA of arthritis + PsO, and C-reactive protein (CRP); *involves more complex calculations*
- Clinical Disease Activity Index for PsA (cDAPSA)[2]: peripheral joints, pt pain, pt GA of arthritis; variation of the DAPSA excluding CRP; *improved ease of use but assesses only peripheral joint disease*
- Investigator's Global Assessment of PsO (IGA)[3]: 5-point scale (0=clear; 4=severe); *simple to use but assesses only skin symptoms*

A novel composite endpoint, cDAPSA low disease activity (LDA; score ≤13) + IGA 0 or 1 (0/1; 0=none/1=minimal), has been proposed as a tool for evaluating both joint and skin disease activity in routine clinical practice

Objective

To assess cDAPSA LDA + IGA 0/1 performance, data from the Phase 3 DISCOVER-1 and -2 studies were utilized to:
- **Compare achievement of cDAPSA LDA + IGA 0/1 between pts receiving guselkumab (GUS) vs. placebo (PBO)**
- **Contrast performance of cDAPSA LDA + IGA 0/1 vs. PASDAS LDA**
- **Assess association between earlier cDAPSA LDA + IGA 0/1 response and future stringent disease control**

Methods

DISCOVER-1 and DISCOVER-2 Trial Designs

DISCOVER-1 (W0-W60)[4]	DISCOVER-2 (W0-W112)[5]
Randomized 1:1:1 (N=381)	Randomized 1:1:1 (N=739)
GUS 100 mg at W0, W4, then Q4W GUS 100 mg at W0, W4, then Q8W PBO Q4W through W20; GUS 100 mg at W24 and then Q4W	
History of, or current, PsO ≥3 SJC and ≥3 TJC CRP ≥0.3 mg/dL	History of, or current, PsO ≥5 SJC and ≥5 TJC CRP ≥0.6 mg/dL
~31% of pts previously received 1-2 TNFi	Naïve to biologic agents and JAKi

CRP=C-reactive protein; GUS=Guselkumab; JAKi=Janus kinase inhibitor; PBO=Placebo; PsO=Psoriasis; Q4W=Every 4 weeks; Q8W=Every 8 weeks; SJC=Swollen joint count; TJC=Tender joint count; TNFi=Tumor necrosis factor inhibitor; W=Week.

Assessments and Statistical Methods

- Post hoc analyses: pooled DISCOVER-1 and -2 data through W52 among pts with cDAPSA >13 and IGA >1 at baseline (BL)
- cDAPSA LDA + IGA 0/1 and PASDAS LDA response rates:

Endpoint	Definition	1st Assessed
cDAPSA LDA + IGA 0/1	cDAPSA ≤13 + IGA 0 (clear skin) or 1 (minimal) among pts with cDAPSA >13 and IGA >1 at BL	W16
PASDAS LDA	PASDAS ≤3.2 among pts with cDAPSA >13 and IGA >1 at BL	W8

  - Nonresponder imputation (NRI): W0-24 (pts who discontinued study agent or initiated protocol-prohibited PsA treatments); W0-52 (pts with missing data)
  - Compared between GUS and PBO using logistic regression adjusted for prior TNFi use, and BL cDAPSA, IGA, and conventional synthetic disease-modifying antirheumatic drug (csDMARD) use
- Agreement between cDAPSA LDA + IGA 0/1 and PASDAS LDA (observed data; standard reference: PASDAS LDA):
  - Cohen's kappa, % concordance, sensitivity, and specificity
- Predictive value of W16 cDAPSA LDA + IGA 0/1 or PASDAS LDA for achieving stringent disease control at W52:
  - Logistic regression adjusted for prior TNFi use and BL disease activity/csDMARD use; odds ratio and 95% confidence interval (OR [95% CI]) comparing W52 response rates for W16 responders and nonresponders

Measures of Stringent Disease Control at W52

Measure	Outcome
ACR50/70	Improvement ≥50%/70% in ACR criteria
PASI 100	100% improvement in PASI
PtGA	≤20[a]
HAQ-DI	≤0.5[a]
MDA	≥5 out of 7 criteria[a,b]

[a]Assessed in pts not meeting criteria at BL. [b]Achievement of MDA is defined as meeting 5 out of 7 criteria: TJC ≤1; SJC ≤1; PASI ≤1; pt pain visual analog scale of ≤15; PtGA (arthritis and PsO) visual analog scale of ≤20; HAQ-DI score ≤0.5; and tender entheseal points ≤1. ACR=American College of Rheumatology; BL=Baseline; HAQ-DI=Health Assessment Questionnaire-Disability Index; MDA=Minimal disease activity; PASI=Psoriasis Area and Severity Index; PtGA=Patient Global Assessment; SJC=Swollen joint count; TJC=Tender joint count; W=Week.

Key Takeaways

In a cohort of pts with PsA and cDAPSA >13 + IGA >1 at BL:

- ✓ GUS was associated with early, significant, and durable reductions in peripheral joint + skin disease activity when assessed using the novel composite endpoint of cDAPSA LDA + IGA 0/1
- ✓ Achievement of cDAPSA LDA + IGA 0/1 with GUS was comparable to that of DAPSA LDA + IGA 0/1 determined in previous cohort analyses[6]
- ✓ The novel composite endpoint, cDAPSA LDA + IGA 0/1, showed convergent validity and may be a practical tool for predicting later stringent control of PsA

Results

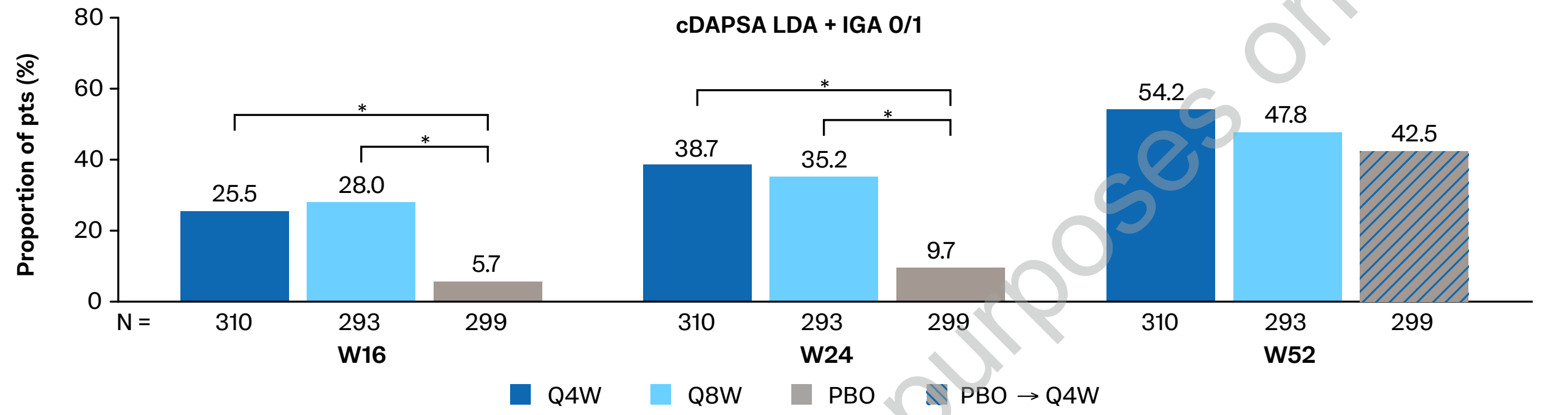
BL characteristics of this PsA cohort with cDAPSA >13 and IGA >1 (~81% of DISCOVER-1 and -2 pts) were generally well balanced across treatment groups

DISCOVER-1 and -2 Pts with cDAPSA >13 and IGA >1	GUS Q4W (N=310)	GUS Q8W (N=293)	PBO (N=299)
Demographics			
Age, y	46.7 (11.3)	46.3 (11.6)	46.2 (11.1)
Male, n (%)	176 (56.8)	163 (55.6)	152 (50.8)
BMI, kg/m^2	29.5 (5.8)	29.3 (6.4)	29.3 (6.3)
PsA duration, y	6.0 (6.0)	5.5 (5.8)	6.5 (6.5)
PsA Characteristics			
SJC [0-66]	11.5 (7.6)	11.7 (8.1)	11.8 (7.0)
TJC [0-68]	20.7 (13.4)	20.4 (12.7)	21.1 (12.9)
PASI [0-72]	12.1 (11.4)	11.3 (11.7)	10.5 (9.8)
IGA [0-4], n (%)			
Mild (2)	131 (42.3)	129 (44.0)	141 (47.2)
Moderate (3)	139 (44.8)	135 (46.1)	133 (44.5)
Severe (4)	40 (12.9)	29 (9.9)	25 (8.4)
CRP, mg/dL	1.5 (1.9)	2.0 (2.5)	2.0 (2.6)
Pt-Reported Outcomes			
Pt pain [VAS 0-100 mm]	60.2 (19.6)	63.4 (19.4)	62.3 (18.8)
PtGA of arthritis [VAS 0-100 mm][a]	66.9 (19.4)	70.4 (18.6)	68.2 (19.3)
HAQ-DI [0-3]	1.2 (0.6)	1.3 (0.6)	1.3 (0.6)
Composite Scores			
DAPSA[b]	46.0 (20.8)	47.1 (20.9)	47.6 (19.6)
cDAPSA [0-154][c]	44.4 (20.4)	45.2 (20.2)	45.5 (19.3)
PASDAS [0-10][d,e]	6.5 (1.1)	6.6 (1.1)	6.6 (1.0)

Data are mean (SD) unless otherwise specified. [a]Q8W N=292. [b]DAPSA disease activity=REM ≤4; LDA >4 to ≤14; ModDA >14 to ≤28; HDA >28; upper limit is undefined. [c]cDAPSA disease activity=REM ≤4; LDA >4 to ≤13; ModDA >13 to ≤27; HDA >27. [d]Q4W N=307; Q8W N=290; PBO N=295. [e]PASDAS disease activity=very low ≤1.9; LDA >1.9 to ≤3.2; ModDA >3.2 to <5.4; HDA ≥5.4. BMI=Body mass index; BL=Baseline; cDAPSA=Clinical Disease Activity Index for PsA; CRP=C-reactive protein; DAPSA=Disease Activity Index for Psoriatic Arthritis; GUS=Guselkumab; HAQ-DI=Health Assessment Questionnaire-Disability Index; IGA=Investigator's Global Assessment; Mod/HDA=Moderate/high disease activity; PASDAS=Psoriatic Arthritis Disease Activity Score; PASI=Psoriasis Area and Severity Index; PBO=Placebo; PsA=Psoriatic arthritis; Pts=Patients; PtGA=Patient Global Assessment; Q4W=Every 4 weeks; Q8W=Every 8 weeks; REM=Remission; SJC=Swollen joint count; SD=Standard deviation; TJC=Tender joint count; VAS=Visual analog scale.

GUS-randomized pts were significantly more likely to achieve cDAPSA LDA + IGA 0/1 at W16 (first timepoint assessed)

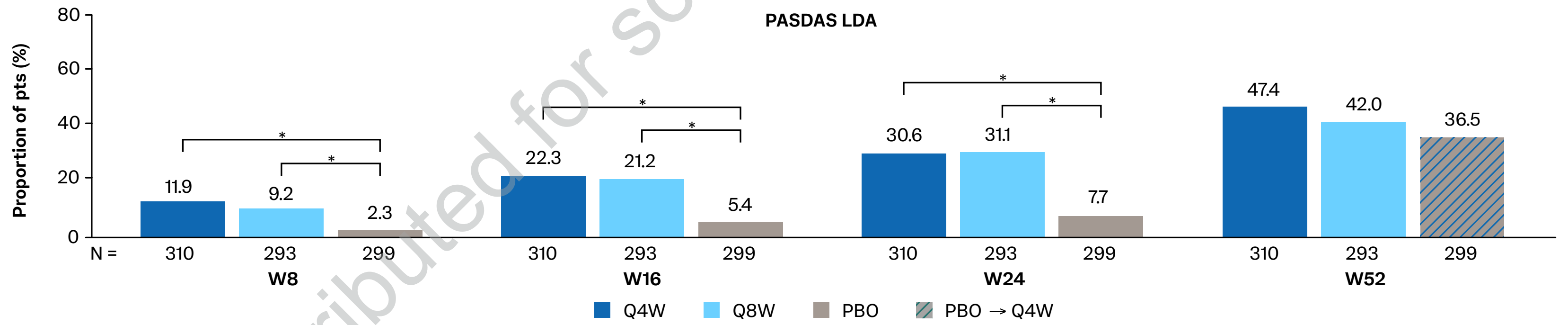
- Rates of achieving cDAPSA LDA + IGA 0/1 increased to 48-54% at W52
- Among GUS-randomized pts not achieving cDAPSA LDA + IGA 0/1 at W16, 18% achieved this response at W24 and 39% did so at W52



Nominal p≤0.001. cDAPSA=Clinical Disease Activity Index for PsA; IGA=Investigator's Global Assessment; LDA=Low disease activity; PBO=Placebo; Pts=Patients; Q4W=Every 4 weeks; Q8W=Every 8 weeks; W16=First timepoint of IGA assessment; W8=First timepoint of PASDAS assessment.

GUS-randomized pts were significantly more likely to achieve PASDAS LDA at W8 (first timepoint assessed)

- Rates of achieving PASDAS LDA increased to 42-47% at W52
- Among GUS-randomized pts not achieving PASDAS LDA at W16, 16% achieved this response at W24 and 34% did so at W52



Nominal p≤0.001. IGA=Investigator's Global Assessment; LDA=Low disease activity; PASDAS=Psoriatic Arthritis Disease Activity Score; PBO=Placebo; Pts=Patients; Q4W=Every 4 weeks; Q8W=Every 8 weeks; W16=First timepoint of IGA assessment; W8=First timepoint of PASDAS assessment.

High (88%) sensitivity and specificity for cDAPSA LDA + IGA 0/1 vs. PASDAS LDA indicated substantial agreement between the novel and established composite endpoints

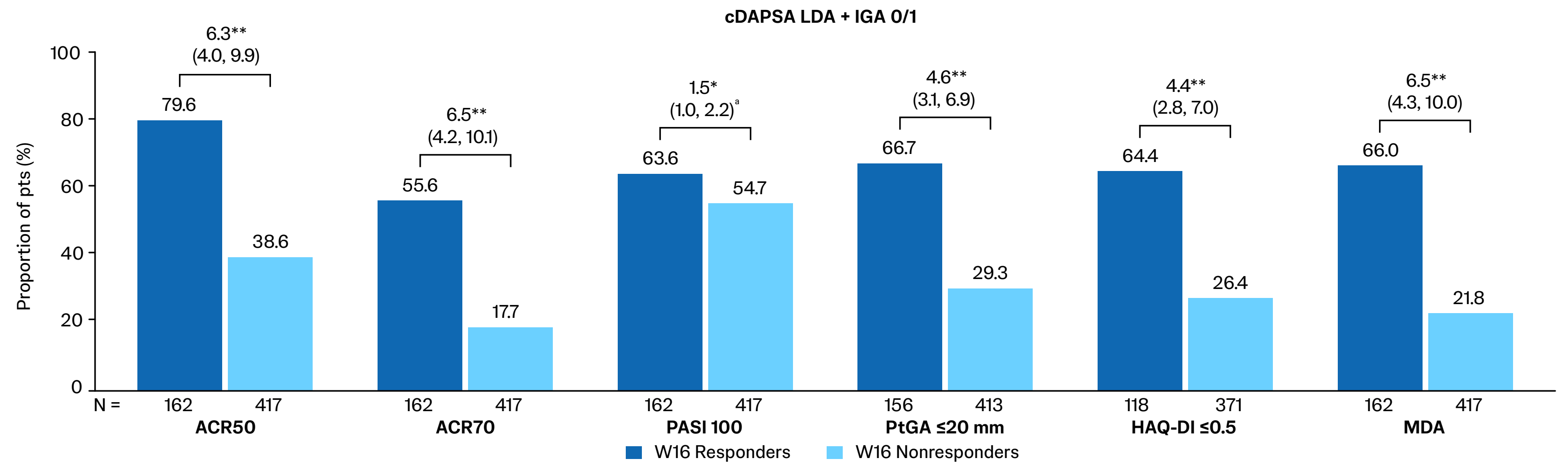
Agreement Between cDAPSA LDA & IGA 0/1 and PASDAS LDA (Standard Reference) Through W52

	Cohen's kappa	Percent (%) concordance	Sensitivity	Specificity
W16	0.70 (0.64-0.76)	0.91 (0.85-0.97)	0.84 (0.78-0.89)	0.92 (0.86-0.98)
W24	0.71 (0.66-0.76)	0.89 (0.83-0.95)	0.87 (0.81-0.92)	0.89 (0.83-0.95)
W52	0.69 (0.64-0.74)	0.85 (0.79-0.90)	0.90 (0.84-0.97)	0.80 (0.75-0.85)
Pooled	**0.72 (0.69-0.75)**	**0.88 (0.85-0.91)**	**0.88 (0.85-0.91)**	**0.88 (0.85-0.92)**

cDAPSA=Clinical Disease Activity Index for PsA; IGA=Investigator's Global Assessment; LDA=Low disease activity; PASDAS=Psoriatic Arthritis Disease Activity Score; W=Week.

GUS-randomized pts achieving cDAPSA LDA + IGA 0/1 at W16 were significantly more likely than nonresponders to achieve more stringent responses across joint, skin, and multidomain outcomes at W52

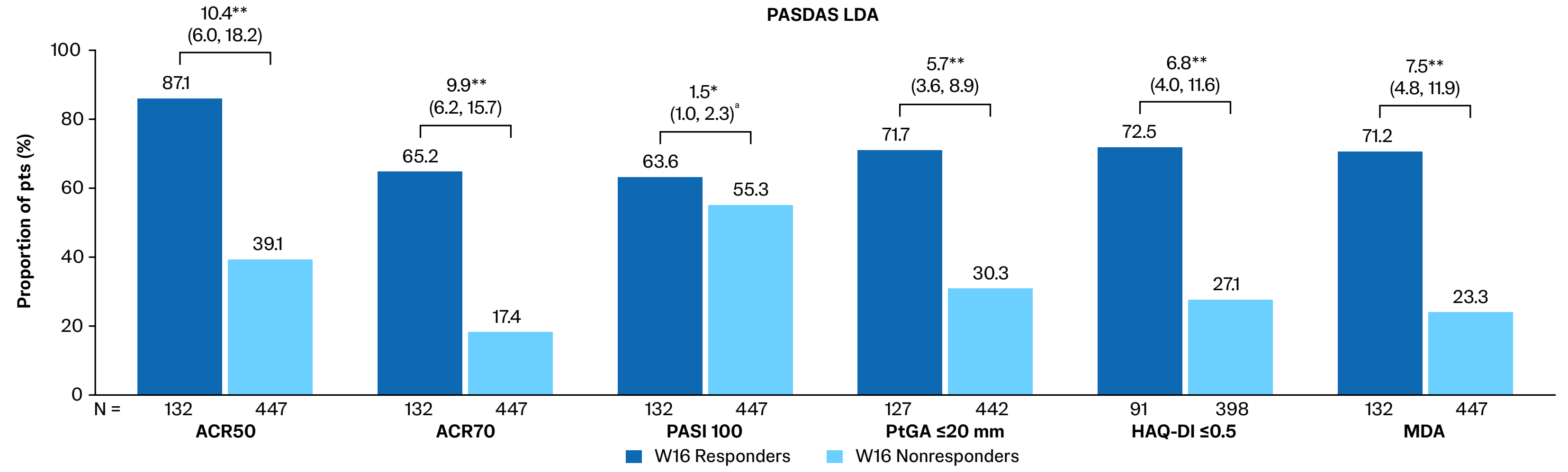
- Among GUS-randomized pts not achieving cDAPSA LDA + IGA 0/1 at W16, 18-55% achieved stringent response outcomes at W52



, nominal p<0.05, <0.001, respectively, derived from logistic regression comparing rates of achieving stringent disease control at W52 for W16 cDAPSA LDA + IGA 0/1 responders vs. nonresponders (OR [95% CI]). [a]95% CI=(1.017, 2.168). ACR=American College of Rheumatology; cDAPSA=Clinical Disease Activity Index for PsA; CI=Confidence interval; HAQ-DI=Health Assessment Questionnaire-Disability Index; IGA=Investigator's Global Assessment; LDA=Low disease activity; MDA=Minimal disease activity; PASI=Psoriasis Area and Severity Index; PtGA=Patient Global Assessment.*

GUS-randomized pts achieving PASDAS LDA at W16 were also more likely than nonresponders to achieve more stringent disease control at W52 across outcomes

- Among GUS-randomized pts not achieving PASDAS LDA at W16, 17-55% achieved stringent response outcomes at W52



, nominal p<0.05, <0.001, respectively, derived from logistic regression comparing rates of achieving stringent disease control at W52 for W16 PASDAS LDA responders vs. nonresponders (OR [95% CI]). [a]95% CI=(1.006, 2.288). ACR=American College of Rheumatology; HAQ-DI=Health Assessment Questionnaire-Disability Index; LDA=Low disease activity; MDA= Minimal disease activity; PASI=Psoriasis Area and Severity Index; PASDAS=Psoriatic Arthritis Disease Activity Score; PtGA=Patient Global Assessment; W=Week.*

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