Biological Sex-Related Differences in Radiographic Progression and Relationship with Early Clinical Response

Post Hoc Analysis of a Phase 3, Randomized, Double-blind, Placebo-Controlled Study in Biologic-Naive Participants with Active Psoriatic Arthritis Treated with Guselkumab

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This presentation was sponsored by Johnson & Johnson.
Presented by Dafna D. Gladman at EULAR 2025; June 11-14, 2025; Barcelona, Spain.

Conflicts of Interest

DDG: Grants: AbbVie, Amgen, Bristol Myers Squibb, Eli Lilly, Johnson & Johnson, Novartis, Pfizer and UCB; Consultant: AbbVie, Amgen, Bristol Myers Squibb, Eli Lilly, Galapagos, Gilead, Johnson & Johnson, Novartis, Pfizer, and UCB.

LE: Grants: AbbVie, Eli Lilly, Fresenius Kabi, Johnson & Johnson, Novartis, Pfizer, and UCB; Consultant: AbbVie, Bristol Myers Squibb, Eli Lilly, Johnson & Johnson, Moolake, Novartis, Pfizer, and UCB.

CS: Grant/Research: AbbVie, Amgen, and Pfizer; Consultant/Speaker: AbbVie, Alfa-Wassermann, Amgen, Biogen, Eli Lilly, EUSA, Galapagos, Johnson & Johnson, Novartis, and SOBI.

PJM: Grants: AbbVie, Acelyrin, Amgen, Bristol Myers Squibb, Eli Lilly, Johnson & Johnson, Novartis, and UCB; Consultant: AbbVie, Acelyrin, Amgen, Bristol Myers Squibb, Century, Cullinan, Eli Lilly, Immagene, Johnson & Johnson, Novartis, Pfizer, Spyre, Takeda, and UCB; Speaker: AbbVie, Amgen, Eli Lilly, Johnson & Johnson, Novartis, Pfizer, and UCB.

AO: Consultant/Advisory Boards: AbbVie, Amgen, Bristol Myers Squibb, Celgene, CorEvitas, Eli Lilly, Gilead, GlaxoSmithKline, Johnson & Johnson, Novartis, Pfizer, and UCB; Grants: AbbVie to Penn, Amgen to Forward/NDB, Novartis to Penn, and Pfizer to Penn; Other Funding: National Psoriasis Foundation, NIAMS, Rheumatology Research Foundation, and University of Pennsylvania.

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LPV: Support for attending meeting: Novartis.

LC: Grant/Research: AbbVie, Amgen, Celgene, Eli Lilly, Johnson & Johnson, Novartis, Pfizer and UCB; Consultant: AbbVie, Amgen, Bristol Myers Squibb, Celgene, Eli Lilly, Gilead, Galapagos, Johnson & Johnson, Moonlake, Novartis, Pfizer, and UCB; Speaker: AbbVie, Amgen, Biogen, Celgene, Eli Lilly, Galapagos, Gilead, GlaxoSmithKline, Johnson & Johnson, Medac, Novartis, Pfizer, and UCB.

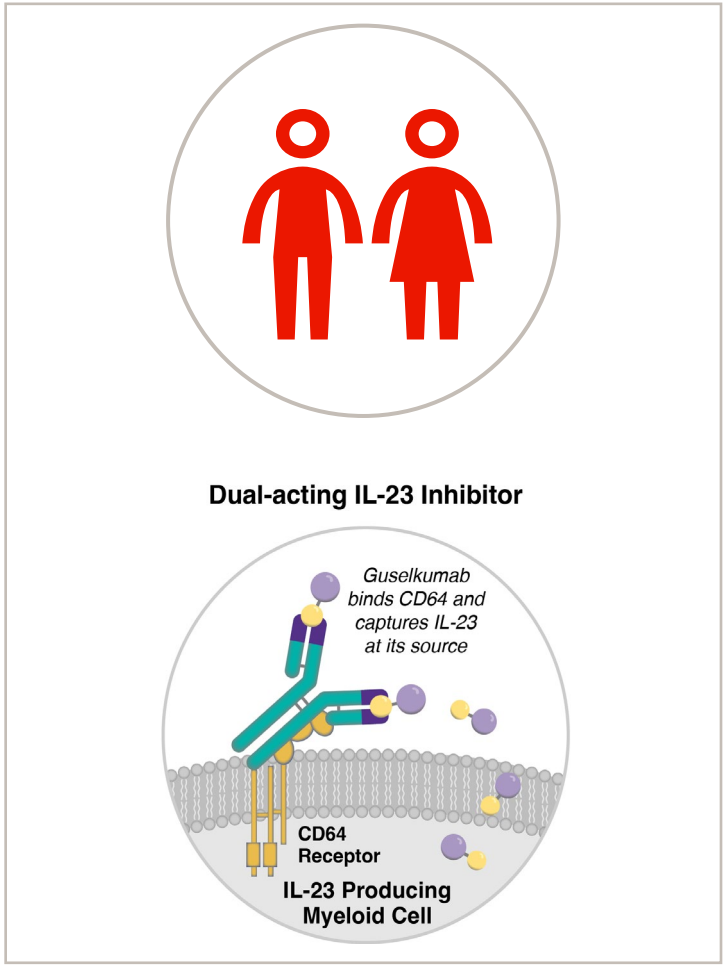
Background

Sex-related differences in PsA

- Real-world studies show that women with PsA have lower treatment response but less joint damage than males[1-4]
- Few RCTs in PsA report sex-disaggregated results

Guselkumab

- Fully human, dual-acting, mAb that selectively inhibits the IL-23p19 subunit[5] and is approved to treat moderate-to-severe plaque PsO, active PsA, and moderately-to-severely active CD and UC[6]
- Only selective IL-23i to significantly inhibit progression of structural damage in pts with active PsA
- Pooled Phase 3 RCTs of guselkumab (GUS; DISCOVER-1 & -2, COSMOS) showed no sex-related differences in clinical response across PsA domains after adjusting for differences at baseline[7]
- DISCOVER-2 assessed radiographic progression in biologic-naïve pts with active PsA



1. Eder L. *Ann Rheum Dis* 2013;72:578-82. 2. Eder L. *Lancet Rheumatol* 2023;5:e716-27. 3. Hojgaard P. *Rheumatol (Oxford)* 2018;57:1651-60. 4. Passia E. *Arthritis Res Ther* 2022;24:22. 5. Sachen KL, et al. *Front Immunol*. 2025; doi: 10.3389/fimmu.2025.1532852. 6. Janssen Biotech, Inc. *U.S. FDA website*. Revised March 2025. 7. Eder L. *Arthritis Rheumatol* 2024;76(suppl 9). **CD=**Crohn's disease, **GUS**=guselkumab, **IL**=interleukin, **mAb**=monoclonal antibody, **pts**=participants, **RCT**=randomized controlled trial, **UC=**ulcerative colitis.

Objective

Conduct post-hoc analyses of DISCOVER-2 pts to determine:

1. Sex-related differences in baseline characteristics
2. Relationship between sex and radiographic progression
3. Relationship between early improvement in joint manifestations and radiographic progression across sexes

pts=participants.

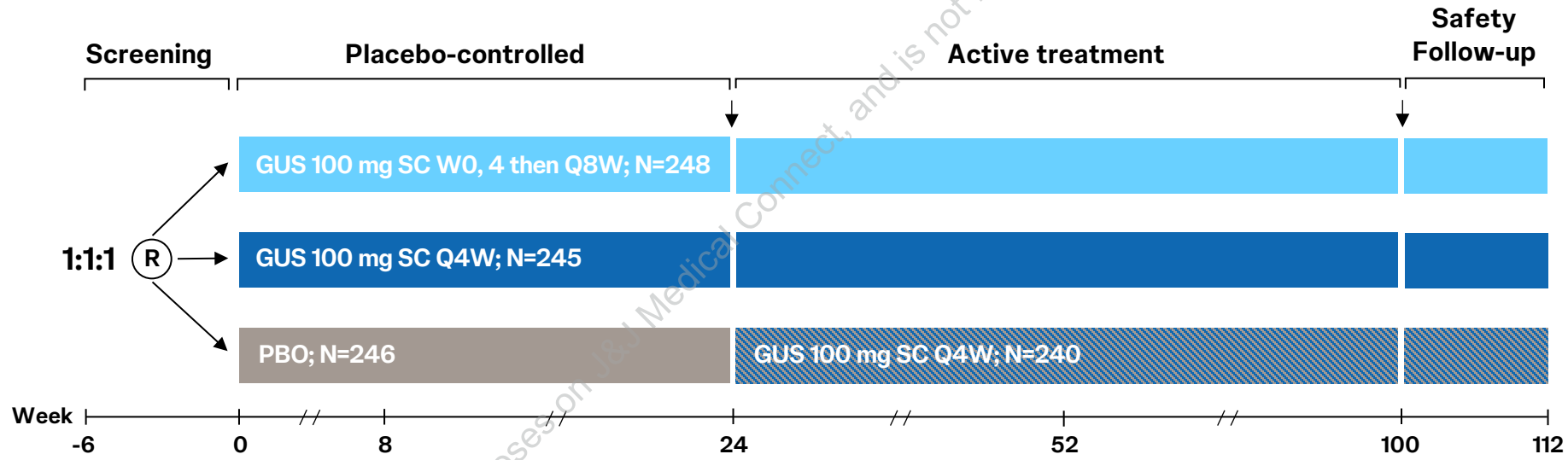
Methods

DISCOVER-2 study design and key outcomes

Key inclusion criteria:

- SJC ≥5
- TJC ≥5
- CRP ≥0.6 mg/dL
- Biologic-naïve

[NCT03158285]



Total PsA-modified vdH-S score

- Measure **of structural damage progression assessed by radiographs of hands and feet through W100**
- **Sum of: Number and size of joint erosions (0-320) + Degree of joint space** narrowing in the hands, wrist, and feet (0-208)

cDAPSA score

- Composite **measure of joint disease activity assessed at W8**
- **Sum of: TJC (0-68) + SJC (0-66) + PtGA arthritis VAS (0-10 cm) + Pt pain VAS (0-10 cm)**
- **cDAPSA LDA/REM: Score ≤13**

cDAPSA=clinical Disease Activity Index for PsA, **CRP=**C-reactive protein, **GUS**=guselkumab, **LDA**=low disease activity, **PBO**=placebo, **PtGA**=patient global assessment, **Q4W**=every 4 weeks, **Q8W**=every 8 weeks, **R**=randomized, **REM**=remission, **SC**=subcutaneous, **SJC**=swollen joint count, **TJC**=tender joint count, **VAS**=visual analog scale, **vdH-S**=van der Heijde-Sharp, **W**=week.

Impact of sex on radiographic progression in DISCOVER-2 pts with active PsA

Objective	Study Cohort	Analyses
Baseline characteristics		
1. Impact of sex	All pts	Continuous variables: 2-sample t-test Categorical variables: Chi-square test
Radiographic progression via Total PsA-modified vdH-S score over W100		
2. Impact of sex	GUS-treated pts	LSM change in **Males** vs **Females** via unadjusted and adjusted[a] MMRMs
3. Impact of early cDAPSA LDA/REM response[b] across sexes		LSM change in **Males** & **Females** via adjusted[a] MMRMs

[a]Adjusted for radiographic progression risk factors + baseline sex-related differences (age, PsA disease duration, BMI, CRP level, presence of dactylitis, non-biologic DMARD use, and baseline levels of outcomes)

[b]Among patients with baseline cDAPSA score >13. **BMI=**body mass index, **cDAPSA**=clinical Disease Activity Index for PsA, **CRP=**C-reactive protein, **DMARD=**disease-modifying antirheumatic drugs, **GUS**=guselkumab, **LDA**=low disease activity, **LSM**=least squares mean, **MMRM**=multivariate mixed models for repeated measures, **pts**=participants, **REM**=remission, **vdH-S**=van der Heijde-Sharp, **W**=week.

Results

Baseline structural damage was similar, but CRP was higher, in male vs female pts

DISCOVER-2 Pt Characteristics at Baseline	Female (N=351)	Male (N=388)	All (N=739)
Demographics			
Age, yrs	46.3 (11.9)	45.1 (11.5)	45.7 (11.7)
Race, White/Asian	97%/3%*	99%/1%	98%/2%
BMI, kg/m^2	29.5 (6.9)*	28.4 (5.4)	28.9 (6.2)
Disease Characteristics			
PsA disease duration, yrs	5.5 (5.9)	5.4 (5.5)	5.5 (5.7)
Total PsA modified vdH-S (0-528)	26.2 (43.1)[a]	25.5 (41.3)[b]	25.8 (42.1)[c]
CRP, mg/dL	1.6 (1.8)****	2.3 (2.8)	2.0 (2.4)

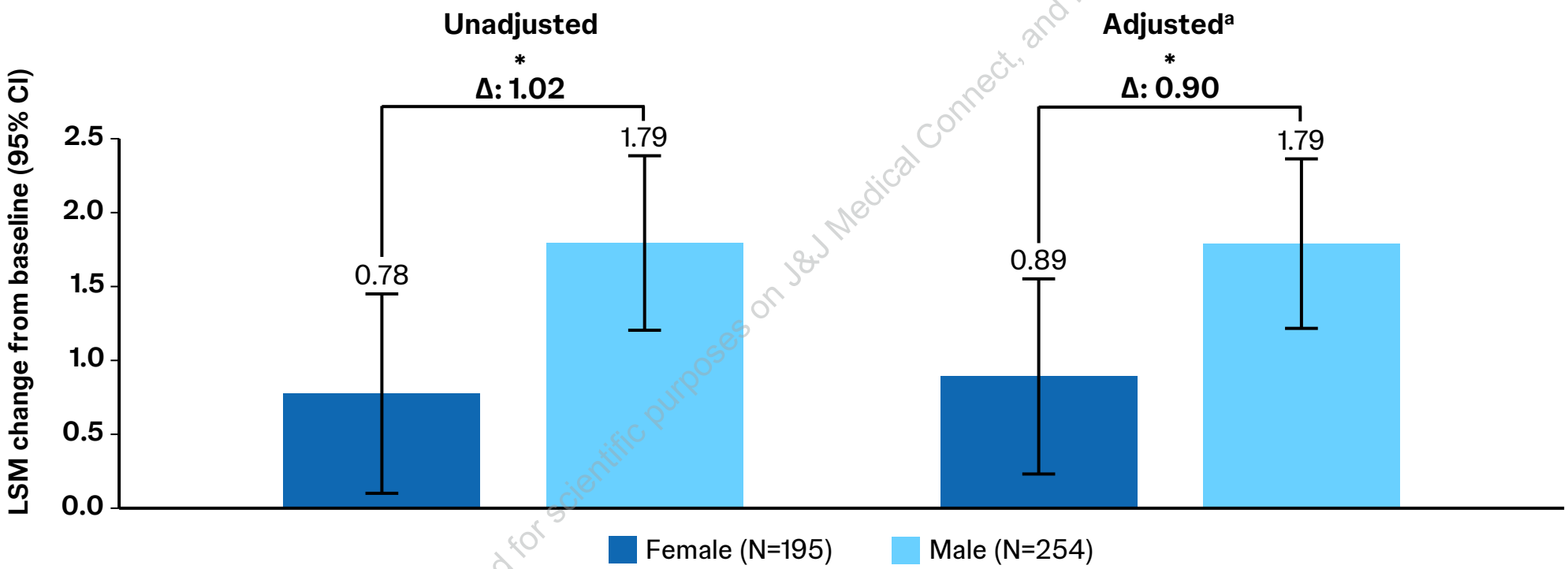
Nominal *p<0.05, **p<0.01, ***p<0.001, and ****p<0.0001 for males vs females. Data shown are mean (SD) unless otherwise indicated. [a]N=305. [b]N=359. [c]N=664. **BMI**=body mass index, **CRP**=C-reactive protein, **pts**=participants, **SD**=standard deviation, **vdH-S**=van der Heijde-Sharp.

Males had more severe psoriasis and more prevalent dactylitis; females reported greater fatigue and functional impairment

DISCOVER-2 Pt Characteristics at Baseline	Female (N=351)	Male (N=388)	All (N=739)
Disease Characteristics			
PASI (0-72)	7.5 (9.1)[a,****]	12.1 (12.3)	9.9 (11.1)[b]
Psoriatic BSA, %	13.7 (17.3)[c,****]	20.8 (22.4)	17.4 (20.4)[d]
cDAPSA (0-154)	46.1 (18.6)	46.4 (20.6)	46.3 (19.7)
Enthesitis[e]	71%[a]	66%	69%[b]
Dactylitis[f]	39%[a,**]	50%	45%[b]
Patient-reported Outcomes			
FACIT-Fatigue (0-52)	28.5 (9.6)[a,***]	30.9 (9.6)	29.7 (9.7)[b]
SF-36 PCS (0-100)	31.9 (7.3)[a,**]	33.6 (7.3)	32.8 (7.3)[b]
HAQ-DI (0-3)	1.4 (0.6)[a,****]	1.2 (0.6)	1.3 (0.6)[b]

Nominal *p<0.05, **p<0.01, ***p<0.001, and ****p<0.0001 for males vs females. Data shown are mean (SD) unless otherwise indicated. [a]N=350. [b]N=738. [c]N=348. [d]N=736. [e]Defined as LEI>0. [f]Defined by DSS>0. **BSA**=body surface area, **cDAPSA**=clinical Disease Activity Index for PsA, **DSS**=Dactylitis Severity Score (0-60), **FACIT**=Functional Assessment of Chronic Illness Therapy, **HAQ-DI**=Health Assessment Questionnaire-Disability Index, **LEI**=Leeds Enthesitis Index (0-6), **PASI**=Psoriasis Area and Severity Index, **pt**=participant, **SD**=standard deviation, **SF-36 PCS**=36-item Short Form Health Survey Physical Component Summary.

Males showed higher rates of radiographic progression at 2 years

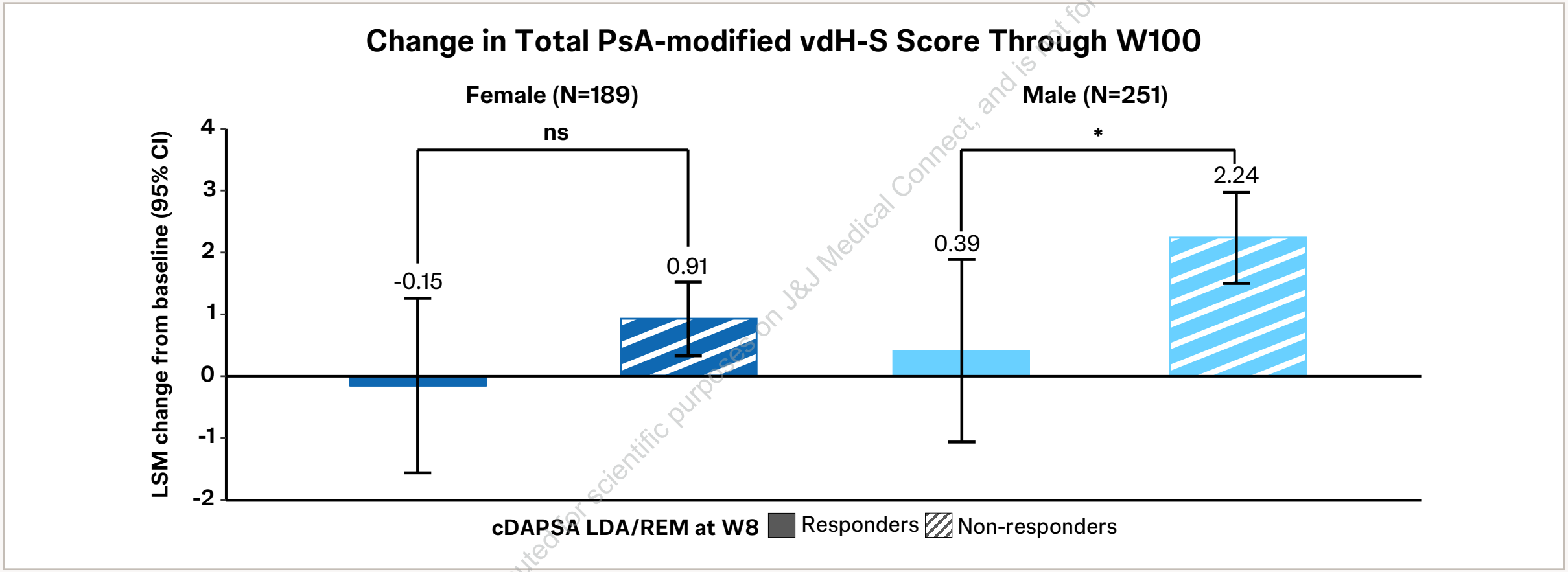


Nominal *p<0.05 for males vs females.

Sex-related differences in radiographic progression were less prominent, but still significant, in adjusted models[a]

[a]Adjusted for known radiographic progression risk factors and sex specific differences in baseline characteristics. **CI**=confidence interval, **LSM**=least square mean, **vdH-S**=Van der Heijde-Sharp, **W**=week.

Across sexes, early (W8) cDAPSA responders had less radiographic progression through 2 years



Nominal *p<0.05 for responders vs non-responders.

The relationship between early cDAPSA response and radiographic progression was stronger among males than females

CI=confidence interval, **cDAPSA**=clinical Disease Activity Index for PsA, **LDA**=low disease activity, **LSM**=least square mean, **ns**=not significant, **REM**=remission, **vdH-S**=van der Heijde-Sharp, **W**=week.

Summary & Conclusions

In DISCOVER-2 biologic-naïve pts with established and active PsA:

- ✓ Males had higher CRP and more prevalent dactylitis - both known risk factors of radiographic progression[1, 2]

- ✓ Males had higher rates of radiographic progression than females
- ✓ Impact of sex on radiographic progression was lower, but still significant, when adjusting for baseline sex disparities

- ✓ Males exhibited a stronger relationship between early improvement in joint disease activity and lower rates of subsequent radiographic progression

Timely and effective treatment is crucial to reduce sequelae of radiographic progression

Phase 3 APEX data provide additional support for GUS as the only selective IL-23i to significantly inhibit radiographic progression and, thus, its use in pts with active PsA at risk of structural damage progression (EULAR 2025 LB 0010[3])

1. van der Heijde D. *J Rheumatol* 2019;46:1089-96. 2. Brockbank JE. *Ann Rheum Dis* 2005;64:188-90. 3. Mease PJ. Late-Breaking Abstract #0010. *EULAR* 2025; June 11-14, Barcelona, Spain. **CRP=**C-reactive protein, **GUS**=guselkumab, **pts**=participants.

Acknowledgment

We respectfully acknowledge the invaluable contributions of the investigators, research staff, and the study participants, whose dedication and commitment made this work possible.