Efficacy of Guselkumab in Bionaïve Psoriatic Arthritis Patients with Severe Disease Activity: Post-Hoc Analysis of a Phase 3, Randomized, Double-Blind, Placebo-Controlled Study

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Background

- Psoriatic arthritis (PsA) is a chronic, autoimmune, heterogeneous disorder with six key domains, including peripheral arthritis, axial disease, enthesitis, dactylitis, and psoriatic skin and nail disease
- Previous analyses of DISCOVER-1 and -2 have shown the fully human IL-23p19-subunit inhibitor guselkumab (GUS) to be associated with robust and sustained improvement in PsA signs and symptoms over 52 weeks (W) in subgroups of patients (pts) across a variety of baseline (BL) demographic and disease characteristics[1]
- In the DISCOVER-2 trial of biologic-naïve pts with active PsA, robust group-level joint and skin response rates and mean improvements from BL in outcome measures were maintained through 2 years[2,3]

Objectives

- **This post-hoc analysis of the 2-year DISCOVER-2 trial evaluated the efficacy of GUS every 4 weeks (Q4W) or Q8W through W100 in biologic-naïve PsA pts with severe BL disease activity based on a range of composite and pt-reported outcomes**

Methods

DISCOVER-2 Trial Design[2,3]
Duration: W0-W112[a]
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; ≥5 SJC and ≥5 TJC; CRP ≥0.6 mg/dL
Naïve to biologic agents and Janus kinase inhibitors

[a]Efficacy was assessed through W100 (study visit window of ±7 days); safety was assessed through W112 (safety visit window of ±14 days). CRP=C-reactive protein; GUS=Guselkumab; PBO=Placebo; PsO=Psoriasis; Q4W=Every 4 weeks; Q8W=Every 8 weeks; SJC=Swollen joint count; TJC=Tender joint count; W=Week.

Severe disease activity for each cohort was defined by the following criteria:

Cohort at BL	Composite and Pt-reported Outcome Measures	Time of First Assessment
cDAPSA >27	SJC, TJC, PtGA, and pt assessment of pain High: >27; moderate: >13 to ≤27; low: >4 to ≤13; remission: ≤4	**W2**
PASDAS ≥5.4	SJC, TJC, dactylitis and enthesitis score, CRP, PhGA, PtGA, and the physical component of the SF-36 High: ≥5.4; moderate: ≥3.2 to <5.4; low: >1.9 to <3.2; very low: ≤1.9	**W8**
PtGA ≥80 mm	VAS 0-100 mm No symptoms: 0; minimal/no disease activity: ≤20; mild: 20 to 40; moderate: 40 to 80; severe: 80 to 100; very severe: 100	**W8**

BL=Baseline; cDAPSA=Clinical Disease Activity Index for Psoriatic Arthritis; CRP=C-reactive protein; PASDAS=Psoriatic Arthritis Disease Activity Score; PhGA=Physician Global Assessment of Disease Activity; Pt=Patient; PtGA=Pt Global Assessment of Disease Activity; SF-36=36-Item Short Form Health Survey; SJC=Swollen joint count; TJC=Tender joint count; VAS=Visual analog scale; W=Week.

In DISCOVER-2 biologic-naïve PsA pts with severe BL disease activity:

- Least squares mean (LSM) changes from BL in the respective outcomes defining each cohort were estimated with mixed models for repeated measures, adjusting for:
  - Treatment group
  - BL score of respective outcome
  - Study stratification factors
    - BL use of conventional synthetic disease-modifying antirheumatic drugs (csDMARDs)
    - High-sensitivity serum C-reactive protein (CRP) concentration
- Clinical Disease Activity Index for Psoriatic Arthritis (cDAPSA) low disease activity or remission (LDA/REM), Psoriatic Arthritis Disease Activity Score (PASDAS) LDA/very low disease activity (VLDA), and Pt Global Assessment of Disease Activity (PtGA) no/minimal disease activity (MDA) response rates through W24 were compared between GUS vs. placebo (PBO) with logistic regression, adjusting for:
  - BL score of respective outcome
  - BL use of csDMARDs
  - High-sensitivity serum CRP concentration
- Response rates through W100 were determined using non-responder imputation (NRI) for missing data
- Maintenance of cDAPSA LDA/REM, PASDAS LDA/VLDA, and PtGA MDA response through W100 was assessed among GUS-randomized pts with observed response at W24

Key Takeaways

- **In DISCOVER-2 biologic-naïve PsA pts with severe disease activity based on cDAPSA, PASDAS, and PtGA scores:**
  - **GUS led to improvements in disease activity that were:**
    - **Clinically meaningful at the first timepoint assessed *(W2 for joint, W8 for overall disease activity)* and significantly greater vs. PBO through W24**
    - **Continuous through W100, representing improvements of ~72-74% in joint disease activity, ~54% in PsA activity across domains, and ~63-66% in pt-reported overall disease activity**
  - **Rates of cDAPSA LDA/REM, PASDAS LDA/VLDA, and PtGA MDA achievement were:**
    - **Significantly greater with GUS vs. PBO at W24**
    - **Maintained at W100 in the vast majority (79-84%) of GUS-randomized pts who achieved response at W24**
- **Findings in PsA pts presenting with severe disease activity support the utility of GUS for inducing early and significant improvement in their disease activity that is durable through W100**

Results

At BL, 88%, 86%, and 29%, respectively, met the cDAPSA, PASDAS, and PtGA criteria for severe disease activity

- BL characteristics were generally consistent across severe disease activity cohorts
- The severe PtGA cohort was characterized by higher average CRP levels; worse joint and skin disease activity, pain, fatigue, and physical function; and less common csDMARD use

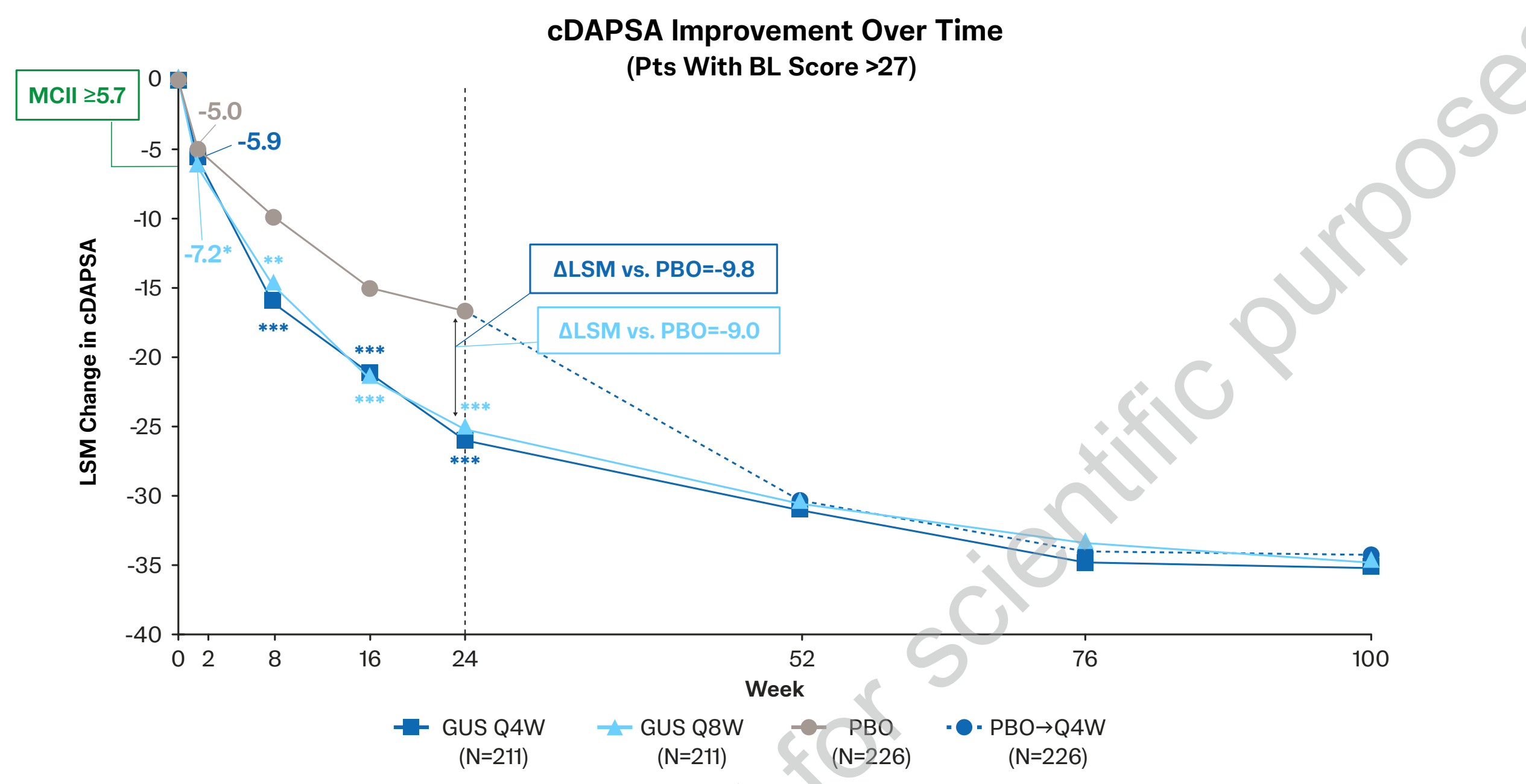
BL Pt Demographics and Clinical Characteristics	cDAPSA >27 (N=648)	PASDAS ≥5.4 (N=639)	PtGA ≥80 mm (N=218)
Pt Demographics			
Age, yrs	45.4 (11.5)	45.5 (11.6)	45.2 (11.2)
Male, %	52%	52%	55%
BMI, kg/m²	28.9 (6.1)	28.9 (6.3)	29.2 (6.6)
PsA Characteristics			
PsA Duration, yrs	5.4 (5.7)	5.4 (5.7)	5.3 (5.7)
SJC (0-66)	13.1 (7.3)	12.8 (7.4)	13.3 (7.8)
TJC (0-68)	23.1 (12.7)	22.5 (12.9)	24.1 (13.5)
CRP, mg/dL	2.0 (2.4)	2.1 (2.5)	2.6 (3.0)
cDAPSA (0-154)	49.5 (18.8)	48.7 (19.4)	53.4 (20.3)
PASDAS (0-10)	6.8 (1.0)[a]	6.8 (0.9)	7.3 (0.9)[b]
PtGA (0-100 VAS)	70.5 (17.5)[c]	71.2 (16.8)	89.0 (6.6)
% BSA with PsO	18.2 (21.1)[d]	18.4 (21.1)[a]	24.4 (25.0)[e]
PASI score (0-72)	10.3 (11.4)[c]	10.4 (11.4)	14.5 (13.4)
Pain (0-100 VAS)	65.5 (17.3)	65.5 (16.9)	77.5 (13.5)
FACIT-Fatigue (0-52)	28.7 (9.4)[c]	28.7 (9.5)	23.8 (9.4)
Medication Use at BL			
csDMARDs	70%	71%	63%
Methotrexate	61%	61%	55%
Corticosteroids	19%	21%	18%
NSAIDs	69%	68%	71%

Data are mean (SD) unless otherwise specified. [a]N=637; [b]N=214; [c]N=647; [d]N=645; [e]N=217. BL=Baseline; BMI=Body mass index; BSA=Body surface area; cDAPSA=Clinical Disease Activity Index for Psoriatic Arthritis; csDMARDs=Conventional synthetic disease-modifying anti-rheumatic drugs; CRP=C-reactive protein; FACIT=Functional Assessment of Chronic Illness Therapy; NSAIDs=Non-steroidal anti-inflammatory drugs; PASDAS=Psoriatic Arthritis Disease Activity Score; PASI=Psoriasis Area and Severity Index; PsO=Psoriasis; PsA=Psoriatic arthritis; Pt=Patient; PtGA=Pt Global Assessment of Disease Activity; SD=Standard deviation; SJC=Swollen joint count; TJC=Tender joint count; VAS=Visual analog scale.

Pts in the severe cDAPSA cohort showed significantly greater improvement in joint disease activity with GUS vs. PBO as early as W2 and through W24

- Minimal clinically important improvements (MCII; ≥5.7) were **achieved as early as W2**
- GUS-treated pts had **~72-74% improvement at W100[a]**

cDAPSA Improvement Over Time
(Pts With BL Score >27)

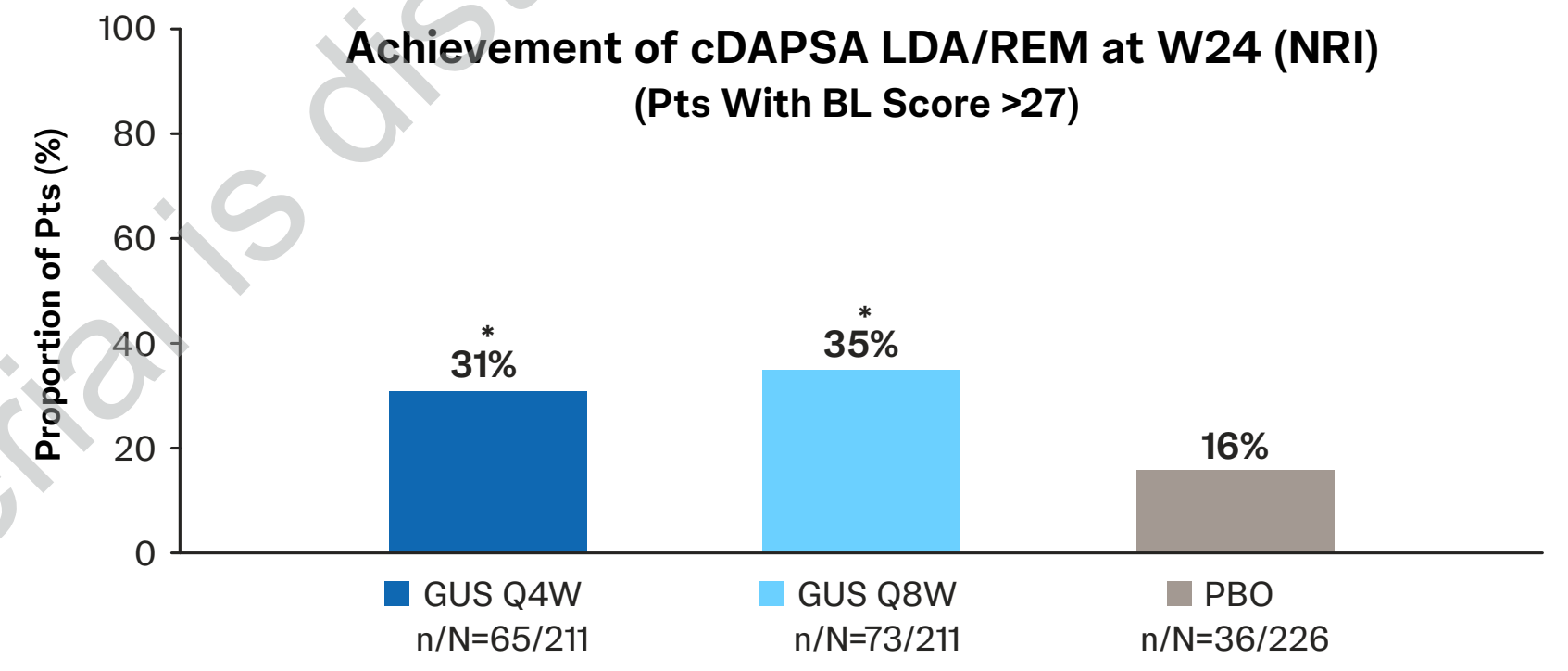


**p<0.05, **p<0.001, ***p<0.0001 for GUS vs. PBO; p-values are nominal. [a]Estimated from mean scores at BL and W100. BL=Baseline; GUS=Guselkumab; cDAPSA=Clinical Disease Activity Index for Psoriatic Arthritis; LSM=Least squares mean; MCII=Minimal clinically important improvements; PBO=Placebo; Pts=Patients; Q4W=Every 4 weeks; Q8W=Every 8 weeks; W=Week.*

A significantly greater proportion of GUS- vs. PBO-treated pts achieved cDAPSA LDA/REM at W24

- Achievement of cDAPSA LDA/REM at W24 was **maintained by 81-82% of GUS-treated pts through W100**

Achievement of cDAPSA LDA/REM at W24 (NRI)
(Pts With BL Score >27)

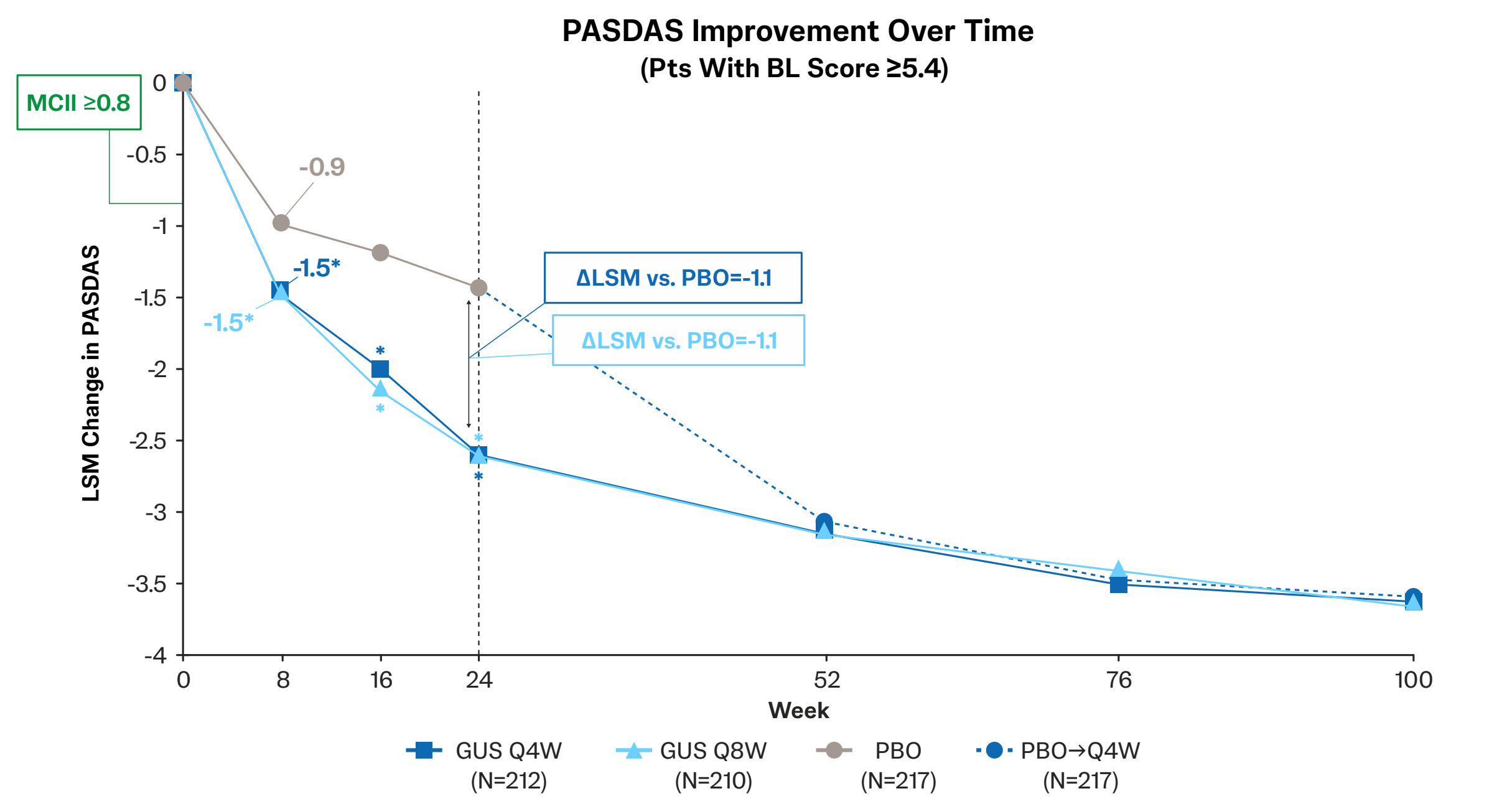


**p<0.0001 for GUS vs. PBO; p-values are nominal. BL=Baseline; cDAPSA=Clinical Disease Activity Index for Psoriatic Arthritis; GUS=Guselkumab; LDA/REM=Low disease activity or remission; NRI=Non-responder imputation; PBO=Placebo; Pts=Patients; Q4W=Every 4 weeks; Q8W=Every 8 weeks; W=Week.*

Pts in the severe PASDAS cohort showed significantly greater improvements with GUS vs. PBO as early as W8 (first timepoint assessed) and through W24

- GUS-treated pts had **~54% improvement in overall disease activity at W100[a]**

PASDAS Improvement Over Time
(Pts With BL Score ≥5.4)

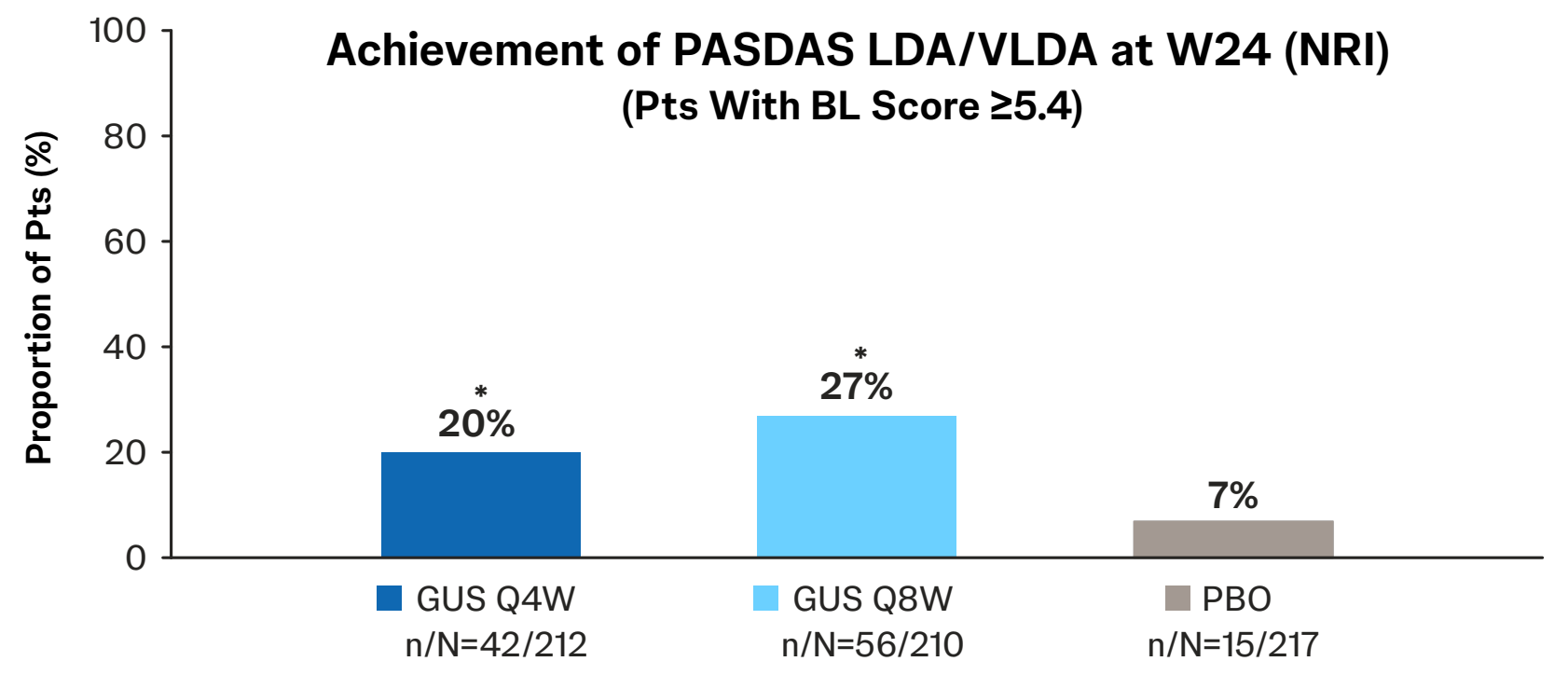


**p<0.0001 for GUS vs. PBO; p-values are nominal. [a]Estimated from mean scores at BL and W100. BL=Baseline; GUS=Guselkumab; LSM=Least squares mean; MCII=Minimal clinically important improvements; PASDAS=Psoriatic Arthritis Disease Activity Score; PBO=Placebo; Pts=Patients; Q4W=Every 4 weeks; Q8W=Every 8 weeks; W=Week.*

A significantly greater proportion of GUS- vs. PBO-treated pts achieved PASDAS LDA/VLDA at W24

- Achievement of PASDAS LDA/VLDA at W24 was **maintained by 79% of GUS-treated pts through W100**

Achievement of PASDAS LDA/VLDA at W24 (NRI)
(Pts With BL Score ≥5.4)

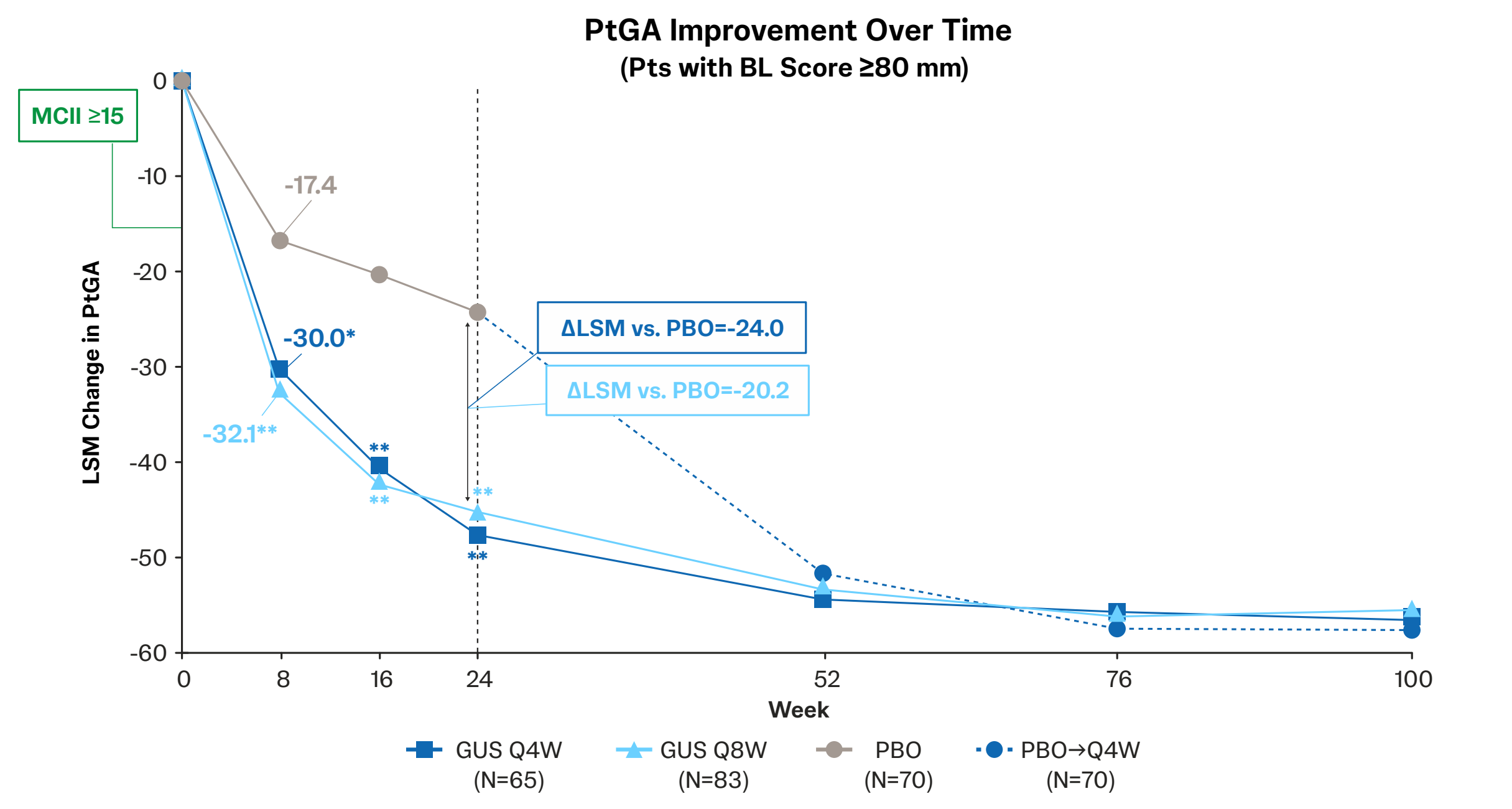


**p<0.0001 for GUS vs. PBO; p-values are nominal. BL=Baseline; GUS=Guselkumab; LDA=Low disease activity; NRI=Non-responder imputation; PASDAS=Psoriatic Arthritis Disease Activity Score; PBO=Placebo; Pts=Patients; Q4W=Every 4 weeks; Q8W=Every 8 weeks; VLDA=Very low disease activity; W=Week.*

Pts in the severe PtGA cohort reported significantly greater improvements with GUS vs. PBO as early as W8 (first timepoint assessed) and through W24

- GUS-treated pts reported **~63-66% improvement at W100[a]**

PtGA Improvement Over Time
(Pts with BL Score ≥80 mm)

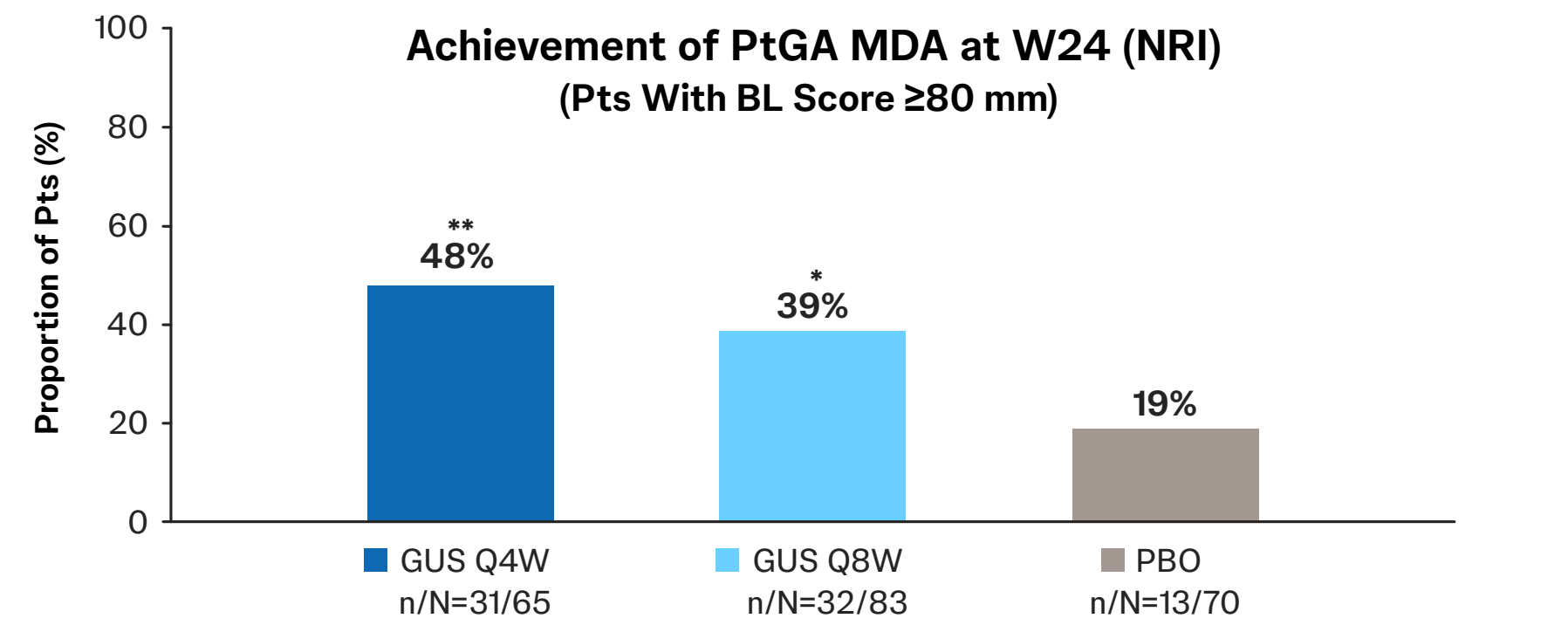


**p<0.01, **p<0.0001 for GUS vs. PBO; p-values are nominal. [a]Estimated from mean scores at BL and W100. BL=Baseline; GUS=Guselkumab; LSM=Least squares mean; MCII=Minimal clinically important improvements; PBO=Placebo; Pts=Patients; PtGA=Pt Global Assessment of Disease Activity; Q4W=Every 4 weeks; Q8W=Every 8 weeks; W=Week.*

A significantly greater proportion of GUS- vs. PBO-treated pts achieved PtGA MDA at W24

- Achievement of PtGA MDA at W24 was **maintained by 81-84% of GUS-treated pts through W100**

Achievement of PtGA MDA at W24 (NRI)
(Pts With BL Score ≥80 mm)



**p<0.01, **p<0.001 for GUS vs. PBO; p-values are nominal. BL=Baseline; GUS=Guselkumab; MDA=Minimal disease activity; NRI=Non-responder imputation; PBO=Placebo; Pts=Patients; PtGA=Pt Global Assessment of Disease Activity; Q4W=Every 4 weeks; Q8W=Every 8 weeks; W=Week.*

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