Guselkumab for the Treatment of Moderate-to-Severe Plaque Psoriasis in Pediatric Patients: Results of a Phase 3, Randomized, Placebo-Controlled Study

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Background/Objectives

Pediatric Plaque Psoriasis (PsO)

- Approximately one-third of patients with plaque PsO report onset before adulthood[1]
- Children/adolescents with plaque PsO have fewer highly effective and safe treatment options than adults and, notably, none that specifically target interleukin (IL)-23[1]

Guselkumab (GUS)

- A fully human monoclonal antibody that selectively inhibits IL-23 by targeting its p19 subunit
- Shown to be highly effective for treating adults with moderate-to-severe plaque PsO[2,3], with a safety profile similar to placebo (PBO)

PROTOSTAR

- Phase 3, randomized, PBO-controlled study with an open-label (OL) reference arm (NCT03451851)
- Evaluated GUS in pediatric participants with moderate-to-severe plaque PsO

[1]Diotallevi F, et al. *Int J Mol Sci*. 2022;23:11128. [2]Blauvelt A, et al. *J Am Acad Dermatol*. 2017;76:405-17. [3]Reich K, et al. *J Am Acad Dermatol*. 2017;76:418-31.
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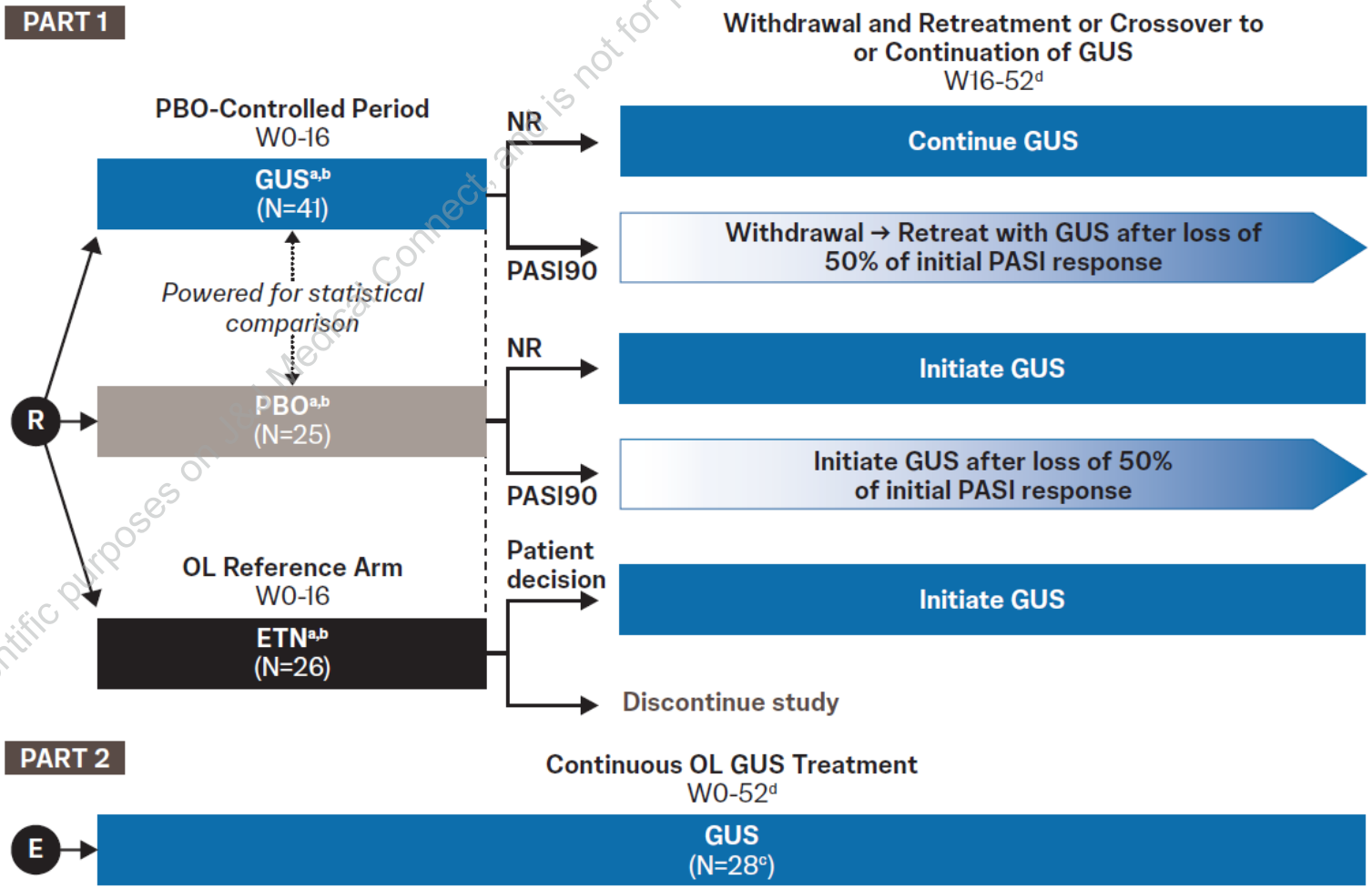
PROTOSTAR – Study Design

Key inclusion criteria:

- ≥6 to <18 years of age, including
  - Children (≥6 to <12 years)
  - Adolescents (≥12 to <18 years)
- Moderate-to-severe plaque PsO for ≥6 months (IGA ≥3; PASI ≥12; ≥10% BSA) **and** ≥1 of the following:
  - Very thick lesions
  - Clinically relevant facial, genital, or hand/foot involvement
  - PASI ≥20, BSA >20% or IGA score=4
- PsO inadequately controlled with phototherapy or topical therapy
- Candidate for phototherapy or systemic therapy
- Not previously treated with etanercept (ETN); candidate for ETN according to approved product labeling



[a]At baseline, participants were randomized to receive PBO or GUS SC (1.3 mg/kg for <70 kg; 100 mg for ≥70 kg) at W0, W4, and W12; or OL ETN SC (0.8 mg/kg up to 50 mg) weekly through W15. Participants who crossed over to GUS after randomization to PBO or ETN received their first dose of GUS at W16 and W20, respectively. [b]Investigators evaluating efficacy were blinded to treatment arm. [c]The number of participants enrolled was dependent on the number of participants randomized to GUS in Part 1, ranging from ≥10 to a number sufficient to ensure ≥100 participants exposed to GUS. [d]Followed by long-term extension.

BSA=body surface area; **E**=enrollment; **IGA**=Investigator's Global Assessment; **NR**=PASI 90 nonresponder; **PASI**=Psoriasis Area and Severity Index; **R**=randomization; **SC**=subcutaneous; **W**=week.

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Outcomes and Analyses

Part 1 (W0-16)	• **Co-primary and major secondary endpoints**
	  • All compared GUS vs PBO at W16
	  • Tested in a predefined, fixed sequence:
	  <u>Co-primary endpoints</u>
	  1. Proportions of participants achieving IGA 0/1 <u>and</u> PASI 75 (or US FDA-required PASI 90)
	  <u>Major secondary endpoints</u>
	  2. Proportion of participants achieving PASI 90 (or US FDA-required PASI 75)
	  3. Proportion of participants achieving IGA 0
	  4. Proportion of participants achieving PASI 100
	  5. Change from baseline in CDLQI*

Part 1 (W16-52)	• Participants entered a period of withdrawal and retreatment or crossover to or continuation of GUS at W16 • Descriptive analyses of endpoints
Part 2 (W0-52)	• Evaluated adolescents receiving continuous GUS in an OL, single-arm design • Descriptive analyses of endpoints
Adverse events (AEs): Summarized through Part 1 W16 and Parts 1 and 2 W52	

***Children's Dermatology Life Quality Index (CDLQI):** Questionnaire for children designed to measure the impact of dermatologic disease on health-related quality of life (HRQoL); scores range from 0-30, with higher scores indicating greater impact.

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Baseline characteristics were generally balanced across treatment cohorts

	PART 1				PART 2
	PBO (N=25)	GUS (N=41)	Ref: OL ETN (N=26)	Total (N=92)	OL GUS (N=28)
Demographics					
Age, yrs	12.4 (3.6)	13.4 (2.9)	12.5 (3.3)	12.9 (3.2)	15.1 (1.6)
Adolescents (≥12 - <18)	60%	76%	62%	67%	100%
Children (≥6 - <12)	40%	24%	38%	33%	0
Male	48%	58%	58%	55%	61%
White	80%	88%	85%	85%	100%
BMI, kg/m^2	22.6 (7.8)	22.0 (5.0)	22.6 (5.2)	22.3 (5.9)	23.1 (4.6)
Disease Characteristics					
Disease duration, yrs	4.5 (2.9)	5.0 (3.1)	4.8 (3.6)	4.8 (3.2)	6.2 (3.1)
BSA (%)	23.4 (9.8)	25.9 (16.8)	22.7 (10.4)	24.3 (13.5)	28.8 (14.1)
IGA					
Moderate (3)	80%	76%	81%	78%	54%
Severe (4)	20%	24%	19%	22%	46%
PASI (0-72)	18.0 (4.4)	19.9 (7.0)	17.9 (5.9)	18.8 (6.1)	21.2 (8.5)
CDLQI (0-30)	9.3 (6.6)	9.4 (7.0)	9.6 (6.6)	9.4 (6.7)	8.3 (7.3)
Prior PsO Treatment					
Topical	100%	100%	100%	100%	100%
Phototherapy[a]	16%	37%	38%	32%	25%
Nonbiologic systemic[b]	28%	34%	31%	32%	46%
Biologic systemic[c]	4%	10%	15%	10%	14%

86% and 96% of participants in Parts 1 and 2, respectively, continued treatment through W52

Data shown are mean (SD), unless otherwise noted. [a]Includes PUVA, UVB. [b]Includes PUVA, methotrexate, cyclosporine, acitretin, apremilast, or tofacitinib. [c]Includes infliximab, alefacept, efalizumab, ustekinumab, briakinumab, secukinumab, ixekizumab, brodalumab, or adalimumab.

BMI=body mass index; **PUVA**=psoralen plus ultraviolet A; **SD**=standard deviation; **UVB**=ultraviolet B.

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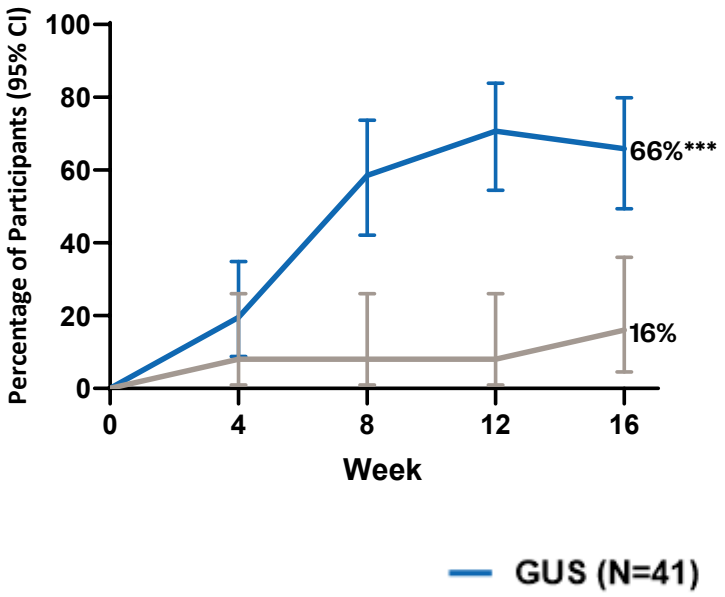
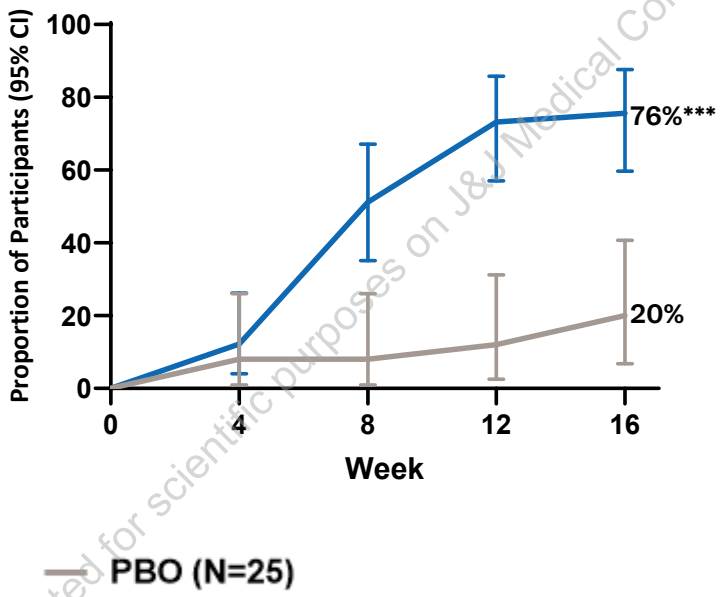
PROTOSTAR W16 co-primary endpoints were met

Co-primary Endpoints (W16)

IGA 0/1



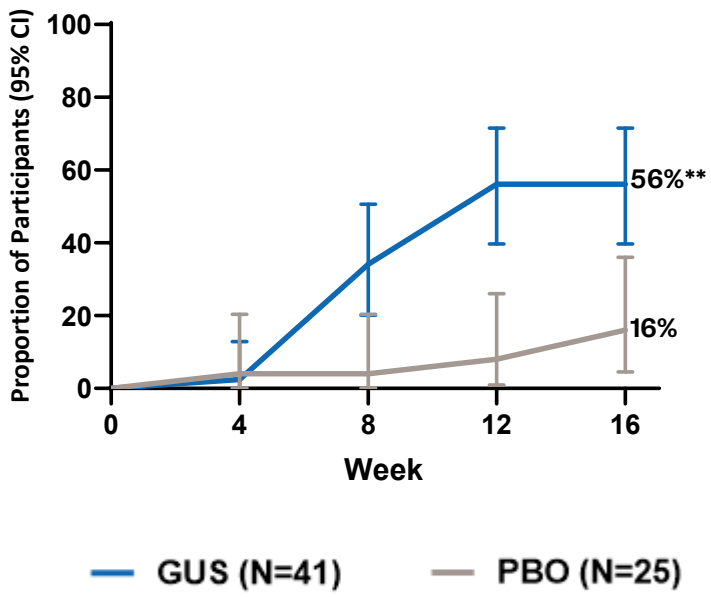
PASI 75



**p<0.01, ***p<0.001 vs PBO

US FDA Co-primary Endpoint (W16)[a]

PASI 90



[a]US FDA-required. P-values represent the comparisons with PBO and are based on the Fisher's exact test stratified by age group and geographic region (pooled). Participants who met treatment failure criteria (discontinued study agent due to lack of efficacy, an AE of worsening PsO, or initiation of a prohibited PsO treatment) or used rescue treatment were considered nonresponders. Participants with missing data were also considered nonresponders after applying treatment failure and rescue treatment rules. **CI**=confidence interval.

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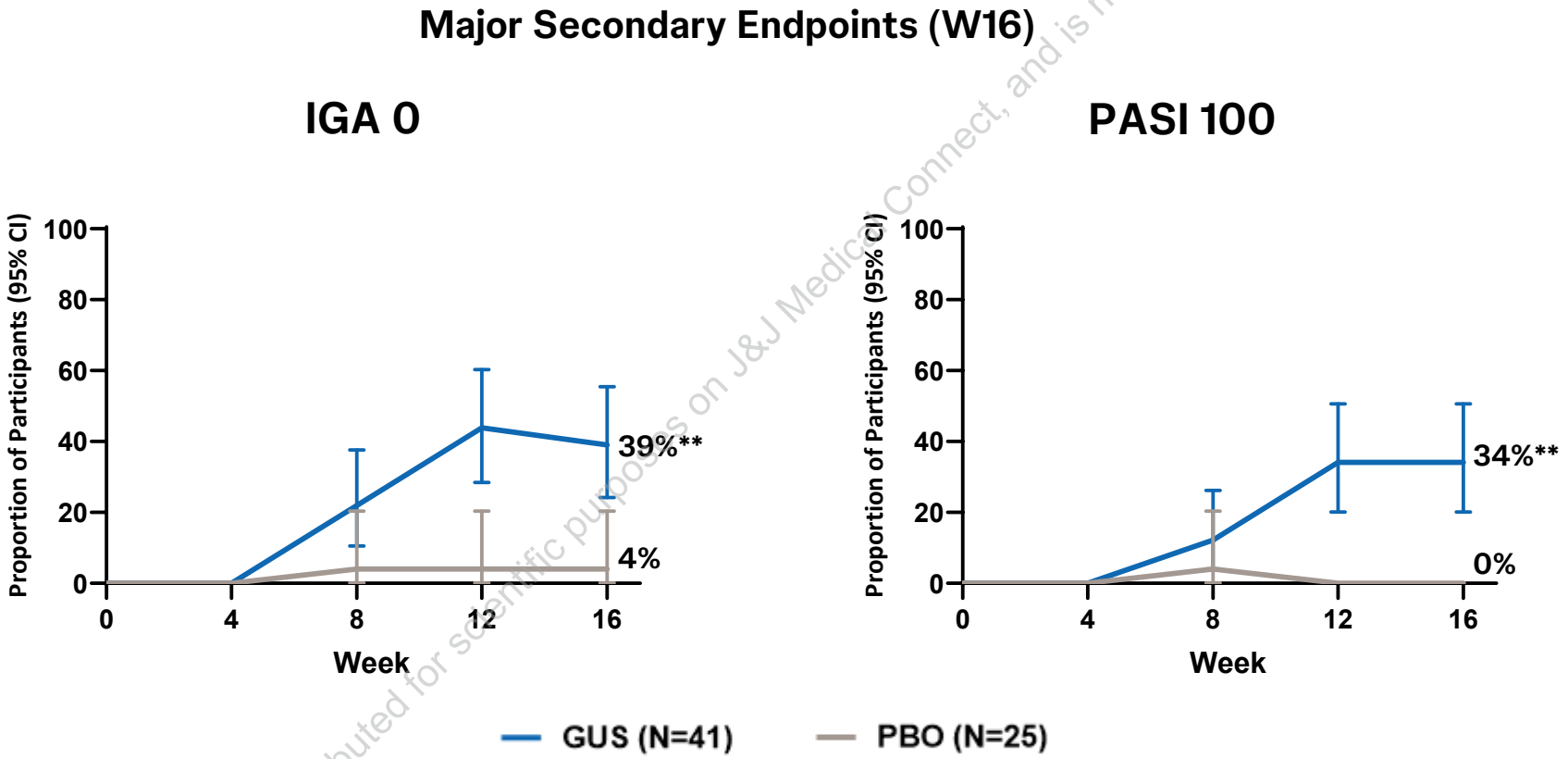
More than one-third of GUS-treated participants achieved completely clear skin at W16



**p<0.01 vs PBO

P-values represent the comparisons with PBO and are based on the Fisher's exact test stratified by age group and geographic region (pooled). Participants who met treatment failure criteria (discontinued study agent due to lack of efficacy, an AE of worsening PsO, or initiation of a prohibited PsO treatment) or used rescue treatment were considered nonresponders. Participants with missing data were also considered nonresponders after applying treatment failure and rescue treatment rules.

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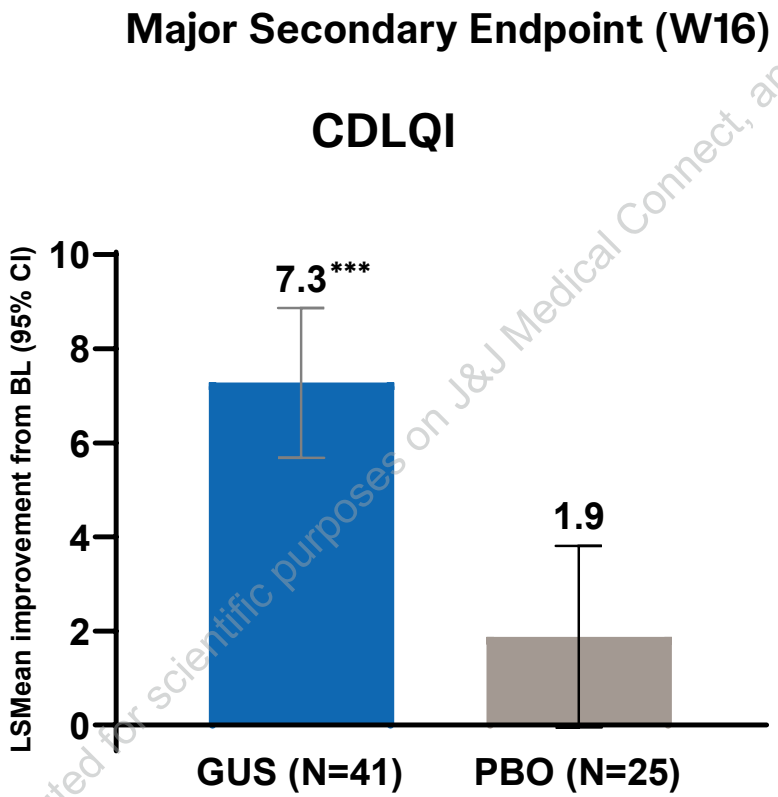
GUS-treated participants reported significantly greater improvement in HRQoL



***p<0.001 vs PBO

P-values test for no difference with PBO from mixed model for repeated measurement (MMRM) model with factors of treatment group, geographic region, age group, baseline CDLQI score, visit, baseline CDLQI score by visit and treatment by visit. Zero change was assigned after participants met treatment failure criteria (discontinued study agent due to lack of efficacy, an AE of worsening PsO, or initiation of a prohibited PsO treatment) or used rescue treatment. Participants with missing data were imputed as zero improvement from baseline.

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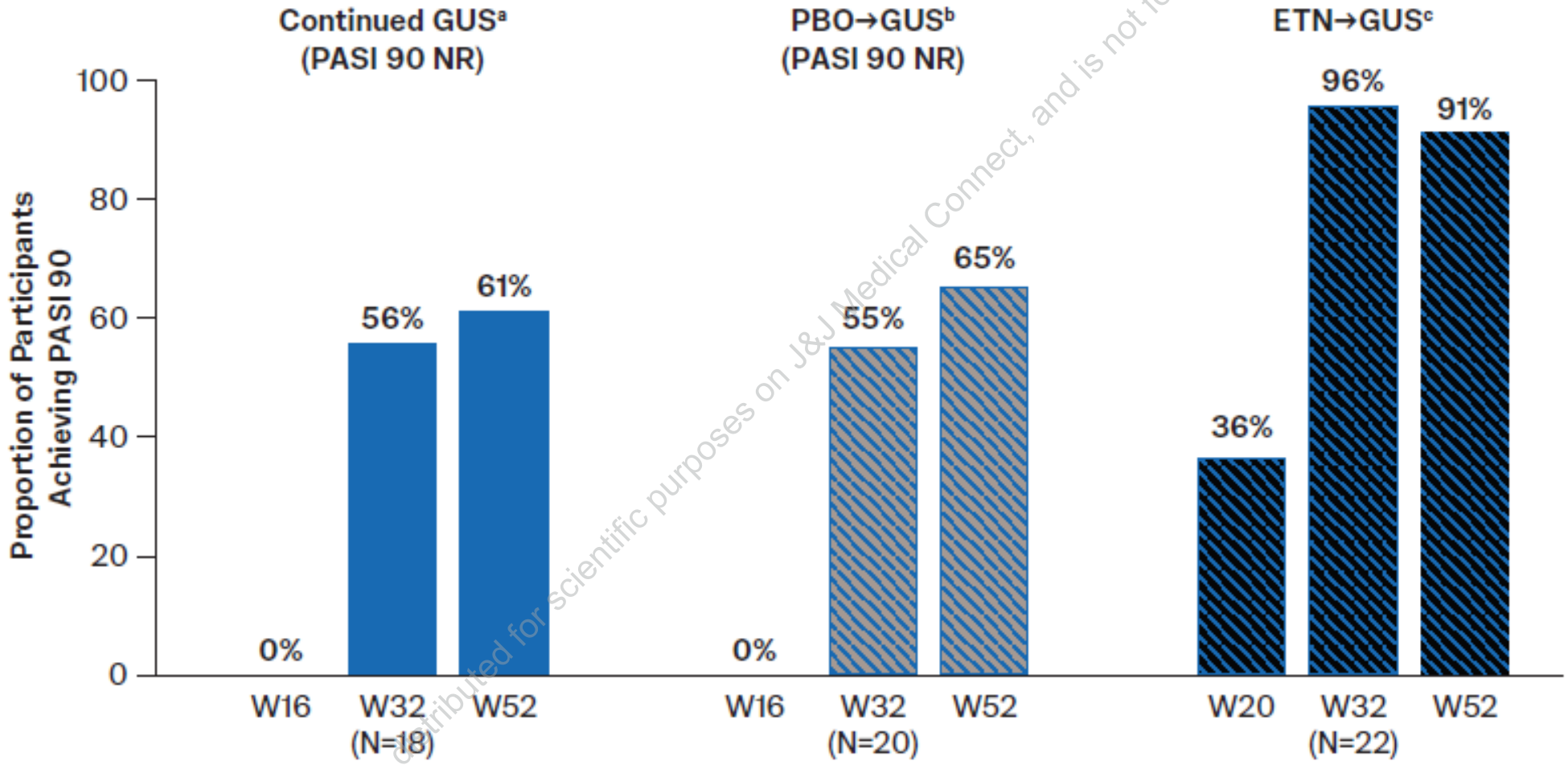
PASI 90 rates markedly increased in W16 PASI 90 NR continuing/initiating GUS or after switching to GUS



[a]Includes participants randomized to GUS at W0 who were PASI NR at W16. [b]Includes participants randomized to PBO at W0 who were PASI 90 NR at W16 and crossed over to receive GUS. [c]Includes participants randomized to ETN at W0 and crossed over to receive GUS.

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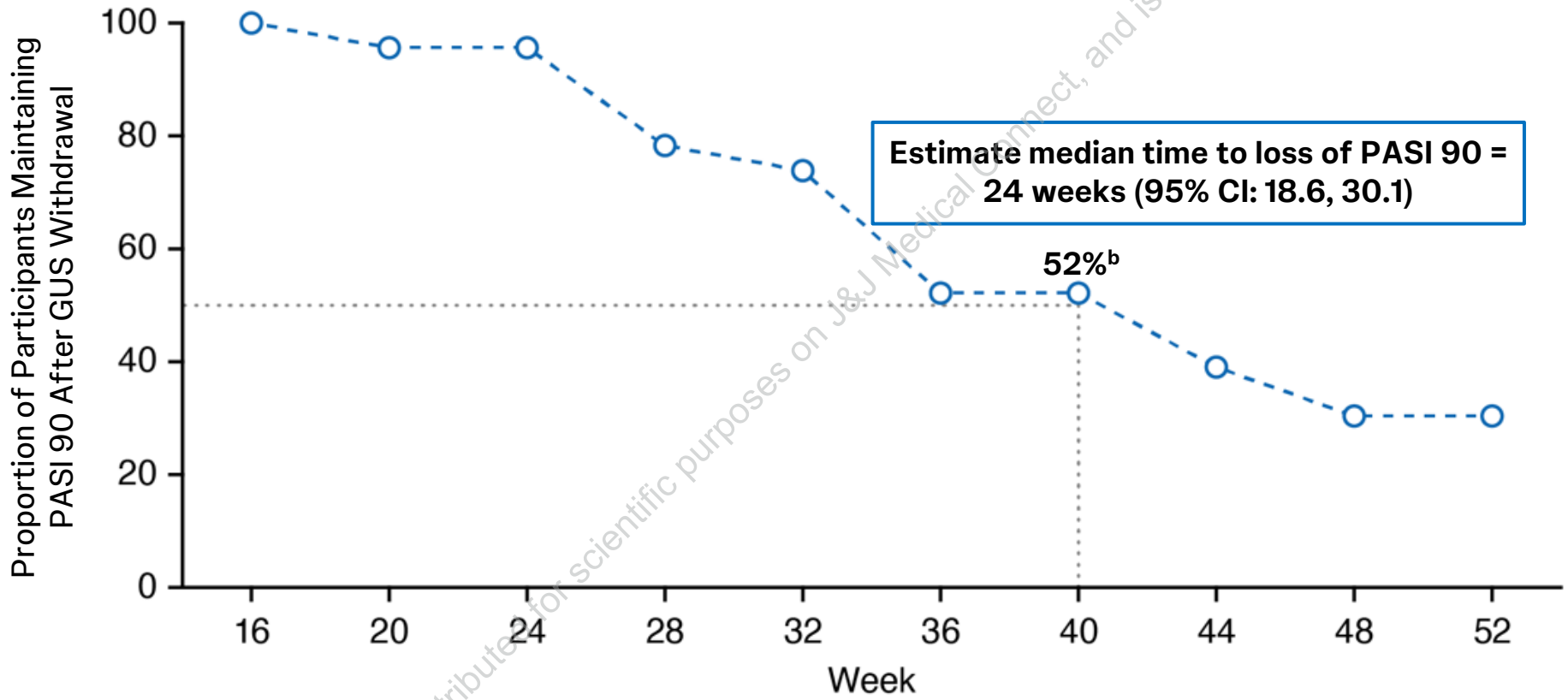
PASI 90 R at W16 maintained response for a median of 24 weeks after GUS withdrawal[a]



[a]Last GUS dose at W12.
[b]Among GUS-randomized participants who were PASI 90 R at W16 and withdrawn from GUS (N=23).
R=responders.
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Continuous OL GUS also provided high rates of improvements that generally increased over time

	PART 2: OL GUS (N=28)	
	W16	W52
Clinician- and Patient-Reported Outcomes		
IGA 0/1	89%	86%
PASI 75	82%	93%
PASI 90	64%	82%
IGA 0	46%	75%
PASI 100	36%	54%
CDLQI, mean (SD) change from baseline[a]	-6.8 (6.32)	-7.3 (6.83)

[a]N=26.

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Through W16, AE rates were generally comparable across groups

	PART 1		
	PBO (N=25)	GUS (N=41)	Ref: OL ETN (N=26)
Adverse Events Through W16			
Mean weeks of follow-up	16.3	16.4	16.1
Mean number of administrations	2.9	3.0	14.9
Participants with ≥1:			
AE	68%	42%	58%
SAE	0	2%[a]	0
AE leading to discontinuation	4%[b]	0	0
Infection	40%	29%	38%
Serious infection	0	0	0

[a]Radius fracture in 1 GUS participant. [b]Worsening PsO in 1 PBO participant.
Participants are counted only once for any given event, regardless of the number of times they experienced the event. AEs are coded using MedDRA Version 26.0.
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No GUS safety signal was identified through 1 year

	PART 1	PART 2
	Total GUS (N=86)	OL GUS (N=28)
Adverse Events Through W52		
Mean weeks of follow-up	41.0	50.8
Mean number of administrations	4.8	6.8
Participants with ≥1:		
AE	72%	82%
SAE[a]	2%	4%
AE leading to discontinuation[b]	1%	4%
Infection	58%	54%
Serious infection	0	0

Most common AEs[c]:

- Nasopharyngitis
- Upper respiratory tract infection
- COVID-19

No participants with:

- Active tuberculosis
- Opportunistic infection
- Malignancy
- Death

[a]Included a radius fracture (GUS group), chronic tonsillitis (crossover from PBO to GUS), and trauma due to a fall (OL GUS). [b]Included pregnancy (GUS group) and suicidal ideation (OL GUS). [c]Part 1 (total GUS group): nasopharyngitis (28%) and upper respiratory tract infection (13%); and Part 2 (OL GUS): nasopharyngitis (25%) and COVID-19 (21%). Participants are counted only once for any given event, regardless of the number of times they experienced the event. AEs are coded using MedDRA Version 26.0.

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Key Takeaways

In the Phase 3 PROTOSTAR study of GUS in pediatric participants with moderate-to-severe plaque PsO:

- ✓ **All co-primary and major secondary endpoints were met; more than one-third of GUS-treated pediatric participants achieved completely clear skin at W16**
- ✓ **Through 1 year, participant retention was robust and response rates to continuous GUS treatment were durable and generally increased**
- ✓ **AE rates for GUS in pediatric participants were generally comparable to PBO through W16**
- ✓ **Through 1 year, no new safety signals were identified in children/adolescents relative to the GUS safety profile established in adults**

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