Guselkumab Pharmacokinetics and Immunogenicity in Pediatric Psoriasis: Phase 3 PROTOSTAR Study

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Background

Guselkumab (GUS)
- A fully human monoclonal antibody that selectively inhibits interleukin-23 by targeting its p19 subunit
- Shown to be highly effective (with dosing of 100 mg at Week [W]0, W4, and every 8 weeks thereafter) for treating adults with moderate-to-severe plaque psoriasis (PsO), with a safety profile similar to placebo (PBO)[1,2]
- In prior studies, mean steady-state trough serum GUS concentration in adult PsO participants (pts) was approximately 1.2 µg/mL

PROTOSTAR
- Phase 3, randomized, PBO-controlled study with an open-label (OL) reference arm in pediatric pts (≥6 to <18 years) with moderate-to-severe plaque PsO (NCT03451851)[3]
- GUS demonstrated significantly greater clinical response rates and similar adverse event rates vs PBO in pediatric PsO pts[3]

Objectives

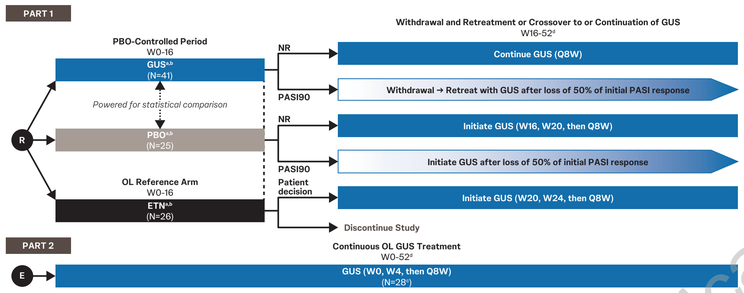
- **Evaluate the pharmacokinetics (PK) and immunogenicity of GUS in pediatric pts with moderate-to-severe plaque PsO from PROTOSTAR**
- **Determine whether PK exposure achieved with pediatric weight-based dosing was comparable with that established for the approved adult dose regimen**

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

Part 1: Co-primary endpoints at W16
- Proportions of pts achieving IGA 0/1 and PASI 75 (or US FDA-required PASI 90)

Weight-based dosing of GUS at W0, W4, and W12, then every 8 weeks (Q8W) thereafter[a]:
- <70 kg: 1.3 mg/kg
- ≥70 kg: 100 mg



[a]At baseline, pts 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. [b]Investigators evaluating efficacy were blinded to treatment arm. [c]The number of pts enrolled was dependent on the number of pts randomized to GUS in Part 1, ranging from ≥10 to a number sufficient to ensure ≥100 pts 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.*

Key Takeaways

Findings from PROTOSTAR showed:

- **Steady-state serum GUS concentration was achieved by W20 and maintained through W44**
- **Similar mean/median W16 serum GUS concentrations were observed for <70 and ≥70 kg body weight groups in pediatric PsO pts**
- **Weight-based dosing of GUS administered to pediatric pts generally achieved drug exposure comparable to adult PsO pts who received the approved standard dosage**
- **Antibodies to GUS were infrequent, low titer, and non-neutralizing**
- **No association was observed between antibody development and GUS PK or reduced clinical efficacy**

Evaluations & Results

PK and Immunogenicity

- Venous blood samples were collected at select time points for the measurement of serum GUS concentrations and detection of antibodies to GUS
- Serum GUS concentrations were summarized over time through W16 (Part 1) and W44 (Part 1 & Part 2)
- Incidence and titers of anti-drug antibodies (ADA) to GUS were summarized through W44 for all pts who received ≥1 dose of GUS and had evaluable serum samples following treatment
- Serum samples that tested positive for ADA to GUS were further characterized to determine if the antibodies that had developed could neutralize the biologic activity of GUS *in vitro* (i.e., neutralizing antibodies to GUS)
- Serum GUS concentrations and clinical response rates were evaluated in the context of immunogenicity results to assess ADA impact on PK and clinical outcomes

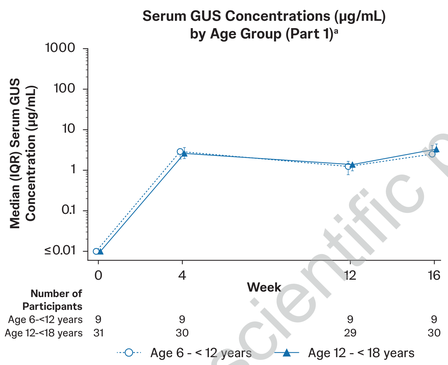
In PROTOSTAR, 41 and 28 pts received GUS[a] in Parts 1 & 2, respectively; no pts <12 years of age were enrolled in Part 2

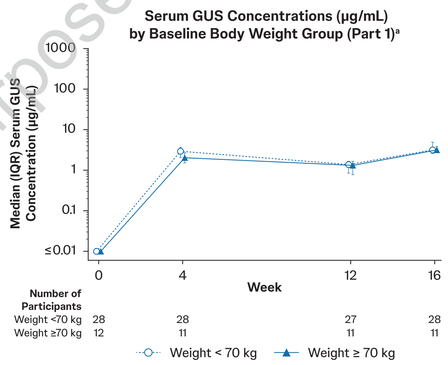
		PART 1 GUS (N=41)	PART 2 OL GUS (N=28)
Demographics			
	Age, yrs	13.4 (2.9)	15.1 (1.6)
	Adolescents (≥12 - <18)	76%	100%
	Children (≥6 - <12)	24%	0
	Male	58%	61%
	White	88%	100%
	Weight, kg	59.4 (20.3)	68.4 (17.3)
	<70	71%	57%
	≥70	29%	43%
	BMI, kg/m^2	22.0 (5.0)	23.1 (4.6)
Disease Characteristics			
	Disease duration, yrs	5.0 (3.1)	6.2 (3.1)
	BSA (%)	25.9 (16.8)	28.8 (14.1)
	IGA		
	Moderate (3)	76%	54%
	Severe (4)	24%	46%
	PASI (0-72)	19.9 (7.0)	21.2 (8.5)
	CDLQI (0-30)	9.4 (7.0)	8.3 (7.3)
Prior PsO Treatment			
	Topical	100%	100%
	Phototherapy[b]	37%	25%
	Non-biologic systemic[c]	34%	46%
	Biologic systemic[d]	10%	14%

Data shown are mean (SD), unless otherwise noted. [a]Through W16. [b]Includes PUVA, UVB. [c]Includes PUVA, methotrexate, cyclosporine, acitretin, apremilast, or tofacitinib. [d]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.*

In Part 1, serum GUS concentrations at W16 were slightly lower in pts ≥6-<12 vs ≥12-<18 years of age; however, ranges largely overlapped

- Mean (median) serum GUS concentrations in pts ≥6-<12 and ≥12-<18 years of age were 2.83 (2.50) and 3.61 (3.34) µg/mL, respectively, at W16
- W16 serum GUS concentrations were similar for the <70 and ≥70 kg groups (mean [median]: 3.53 [3.17] and 3.19 [3.17] µg/mL, respectively)

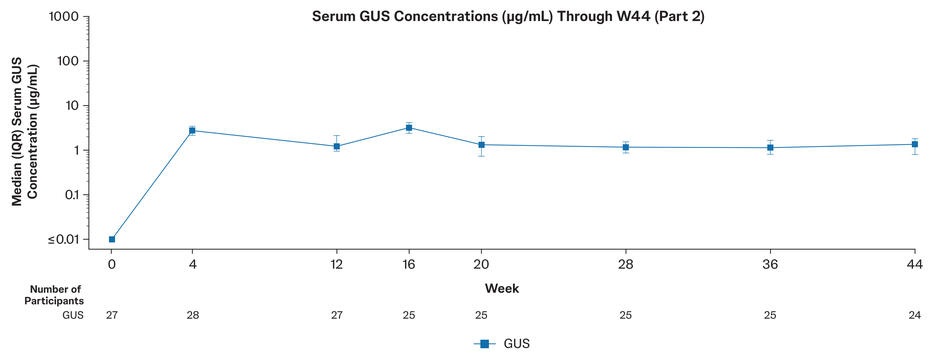




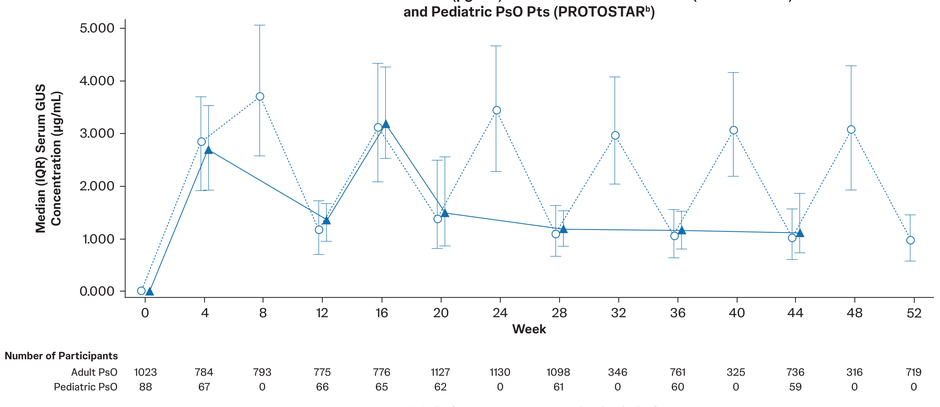
[a]Pts randomized to and treated with GUS. ***IQR****=interquartile range.*

Steady-state was achieved by W20 and maintained through W44

- In Part 2, mean and median trough serum GUS concentrations were similar at W20 and W28, suggesting that serum GUS concentration achieved steady-state by W20 (Part 2 median [IQR] serum GUS concentrations through W44 are shown). Similarly, Part 1 data from pts continuing on GUS confirmed steady-state was achieved by W20 (data not shown).
- In Part 2, W20 mean (median) steady-state trough serum GUS concentrations were similar for the <70 and ≥70 kg groups (1.50 [1.29] and 1.54 [1.47] µg/mL, respectively)



The observed PK for GUS in pediatric PsO pts receiving weight-based dosing was generally comparable with GUS PK in adults with PsO



[a]Pts randomized to adalimumab at W0 are not considered. For VOYAGE 2 only, pts who were randomized to GUS and PASI 90 responders at W28, are excluded after withdrawal from GUS (n=182). [b]Pts randomized to ETN at W0 are not considered. Pts who were randomized to GUS and PASI 90 responders at W16, are excluded after withdrawal from GUS (n=23). Note: For all studies, pts randomized to PBO at W0 who later received GUS are only included at visits where concentrations were collected after those pts received their first dose of GUS (n=20).

In PROTOSTAR, 18.4% of evaluable GUS-treated pts tested positive for ADA to GUS; most were low titer and none were neutralizing

	GUS
Summary of Antibodies to GUS Status Through W44	
Pts with appropriate samples[a]	114
Pts with samples positive for antibodies to GUS, n (%)	
Baseline[b,c]	6 (5.3%)
Postbaseline[c,d]	21 (18.4%)
Peak titers, n	
1:11.25	14
1:22.5	2
1:45	4
1:360	1
Neutralizing antibodies to GUS, n (%)	0 (0%)
Pts negative for antibodies to GUS postbaseline[c,e]	93 (81.6%)

- None of the 21 ADA+ pts had antibodies that were able to neutralize the bioactivity of GUS *in vitro*
- Antibody titers were generally low (95% had titers ≤1:45)
- Development and titers of antibodies to GUS did not impact GUS PK or clinical response

[a]Pts with appropriate samples had 1 or more evaluable samples obtained after their first GUS administration; [b]Pts had samples positive for antibodies to GUS at baseline, regardless of antibody status after their first GUS administration; [c]Denominator is number of pts with appropriate samples for antibodies to GUS; [d]Pts positive for antibodies to GUS includes all pts who had a positive sample (treatment-boosted or treatment-induced) at any time after their first GUS administration through W44. In the instance that a pt had a positive sample at baseline (pre-dose), the pt was considered as positive only if the peak titer of post-treatment samples was ≥2-fold higher than the titer of the baseline sample; [e]Includes all pts whose last sample was negative and excludes pts who were positive for antibodies to GUS through W44.

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