Golimumab Preserves β Cell Function and Reduces Insulin Use in Children and Young Adults With Recently Diagnosed Type 1 Diabetes: The Phase 2 T1GER Study

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Presenter Disclosure

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Background

- T1D is an autoimmune condition characterized by the progressive loss of pancreatic β cells
- T1D onset is often more acute and severe in children than in adults[1,2]
- There are no approved disease-modifying therapies for T1D
- TNFα is a proinflammatory cytokine affecting T1D initiation and progression and resulting in β cell stress and dysfunction
- Golimumab is a human IgG1κ monoclonal antibody specific for TNFα
  - Approved for the treatment of other autoimmune diseases (e.g., RA, UC, nr-axial SpA), including some in children as young as 2 years of age (e.g., polyarticular juvenile idiopathic arthritis)[3,4]

Objective

- To determine if golimumab preserves β cell function and improves diabetes-related clinical and metabolic parameters in children and young adults with newly diagnosed stage 3 T1D

T1D, type 1 diabetes; TNFα, tumor necrosis factor α; RA, rheumatoid arthritis; UC, ulcerative colitis; nr-axial SpA, non-radiographic axial spondyloarthritis.

1. Chiang JL, et al. *Diabetes Care*. 2014;37(7):2034-2054.
2. Kuhtreiber WM, et al. *Diabet Med*. 2015;32(10):1346-1353.
3. SIMPONI (golimumab) injection, for subcutaneous use [package insert]. Horsham, PA: Janssen Biotech, Inc.; 2019.
4. SIMPONI (golimumab) [European Summary of Product Characteristics]. Leiden, The Netherlands; Janssen Biologics B.V.; 2019.

Study Design and Analyses: Phase 2a Study

- Participants were randomized (2:1) to 52 weeks of treatment with SC golimumab or placebo
  - Induction dose of golimumab (<45 kg: 60 mg/m^2 or ≥45 kg: 100 mg) at Weeks 0 and 2
  - Maintenance dose of golimumab (<45 kg: 30 mg/m^2 or ≥45 kg: 50 mg) at Week 4 and every 2 weeks thereafter
- Eligibility criteria included: age 6 to 21 years, T1D diagnosed according to ADA criteria, peak C-peptide level ≥0.2 pmol/mL following a 4-hour MMTT, and randomization within 100 days of diagnosis
  - Participants were to follow the ADA guidelines for HbA1c target[1]
- Primary outcome: 4-hour MMTT C-peptide AUC at Week 52
- Secondary endpoints included:
  - Change from baseline in HbA1c at Week 52
  - Change from baseline in insulin use at Week 52
  - Hypoglycemic event rates (BG ≤70 mg/dL irrespective of clinical symptoms and all events of severe hypoglycemia)*
- Other endpoints included:
  - Change from baseline in 4-hour C-peptide AUC over time
  - Responder analyses
  - Proinsulin/C-peptide ratio over time
- Efficacy and safety analyses were performed on all participants who received ≥1 dose of study drug (ITT)

SC, subcutaneous; ADA, American Diabetes Association; MMTT, mixed-meal tolerance test; AUC, area under the concentration-time curve; ITT, intention-to-treat; BG, blood glucose.
*In addition, post hoc analyses evaluated hypoglycemic event rates by ADA level: Level 1: BG 54-<70 mg/dL; Level 2: <54 mg/dL; Level 3: severe cognitive impairment requiring external assistance for recovery.

1. Chiang JL, et al. *Diabetes Care*. 2014;37(7):2034-2054.

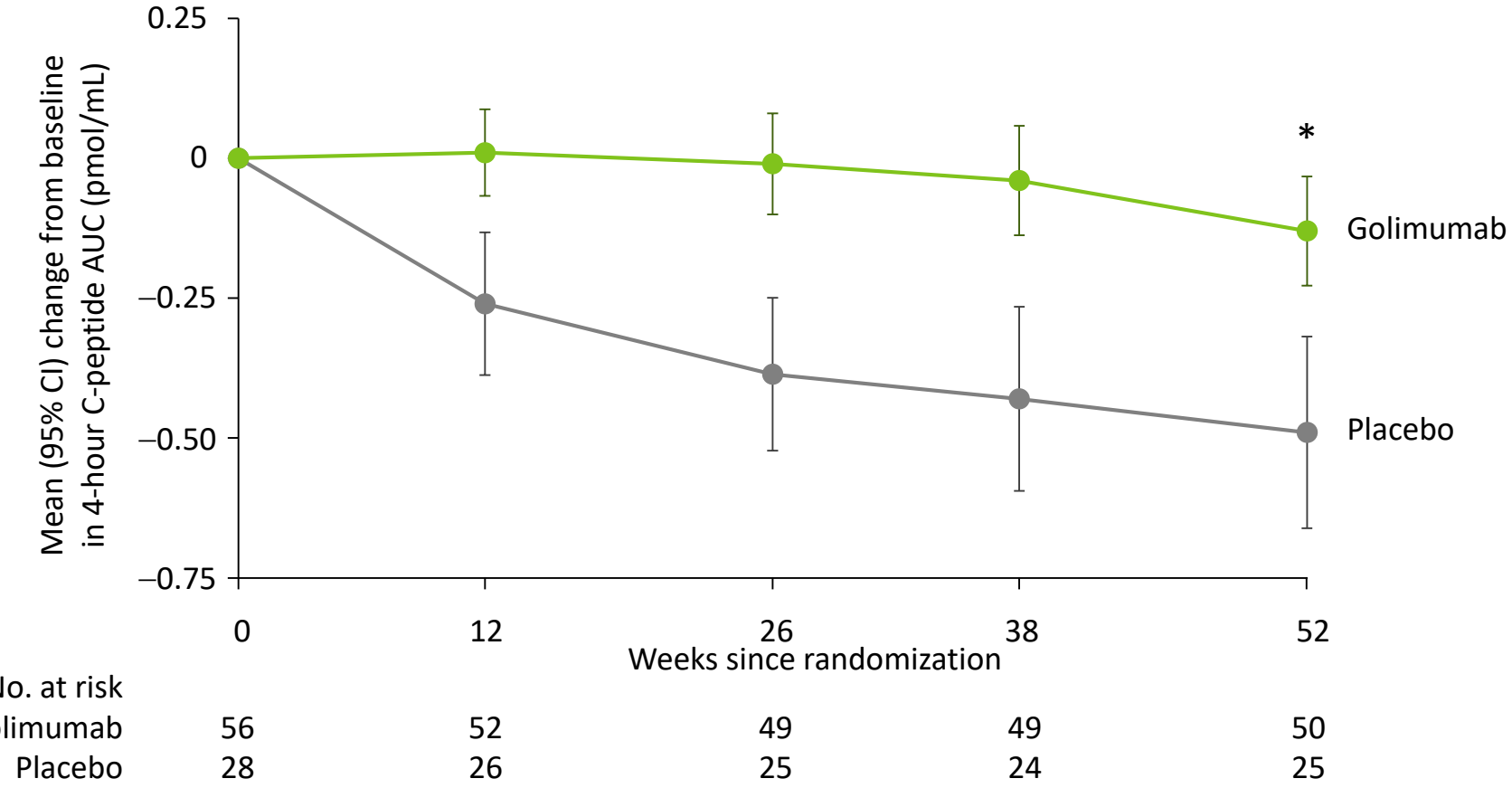
Baseline Characteristics

Characteristic	Golimumab (n = 56)	Placebo (n = 28)
Mean (SD) age, years	14 (4)	14 (4)
6-11 years	36%	29%
12-17 years	48%	46%
18-21 years	16%	25%
Male	55%	64%
Mean (SD) body weight, kg	56 (20)	58 (24)
Mean (SD) days from T1D diagnosis to randomization	74 (20)	75 (19)
Mean (SD) HbA1c, %	7.0 (1.1)	7.1 (1.2)
Mean (SD) daily insulin use, U/kg/day	0.42 (0.26)	0.44 (0.20)
Mean (SD) C-peptide AUC, pmol/mL	0.78 (0.40)	0.88 (0.63)

SD, standard deviation.

Effects on 4-hour C-peptide AUC

- The study met its primary endpoint
- Mean 4-hour C-peptide AUC at Week 52 was 0.64 pmol/mL in the golimumab group and 0.43 pmol/mL in the placebo group (*P* <0.001)
- All sensitivity analyses were consistent with the primary analysis



CI, confidence interval.
**P* <0.001. *P* values were calculated based on a mixed model for repeated measures with post-baseline log(AUC+1) as the response variable, gender, treatment, time, and treatment-by-time interaction as categorical effects, as well as baseline, baseline-by-time, and age as covariates. The baseline value was in log(AUC+1) scale.

HbA1c, Insulin Use, and Hypoglycemic Events

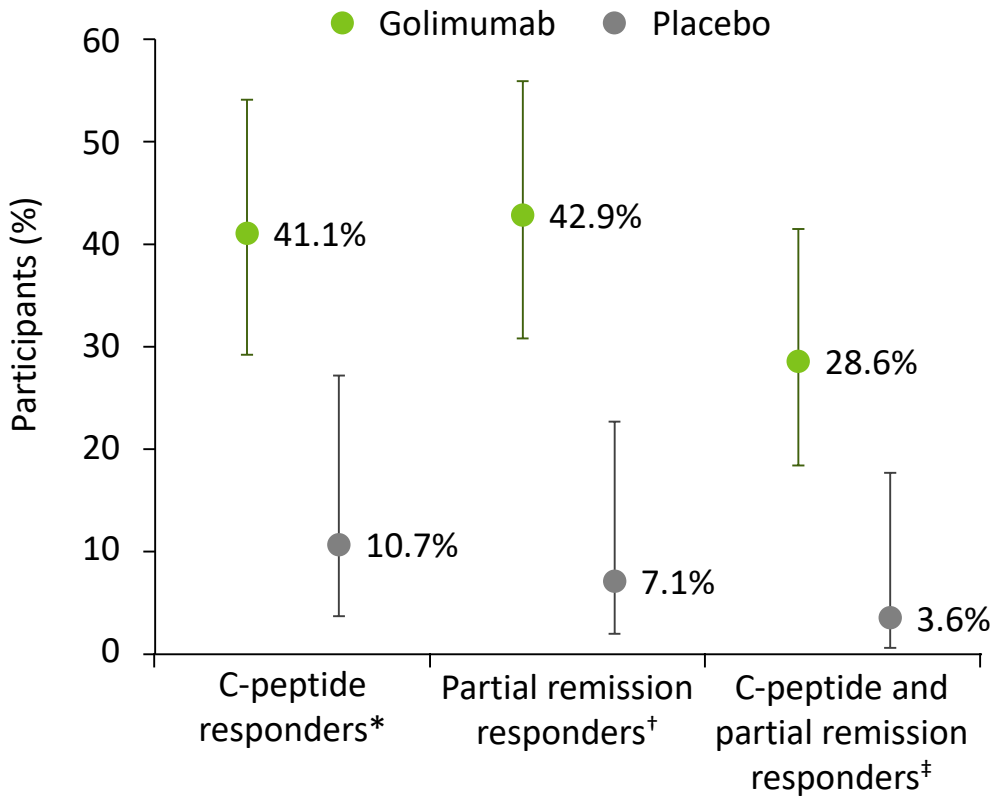
	Golimumab (n = 56)	Placebo (n = 28)	Multiplicity adjusted *P* value*
HbA1c, %			
LS mean change (SE) from baseline at Week 52	0.47 (0.21)	0.56 (0.29)	
Difference for golimumab vs placebo (95% CI)	–0.09 (–0.81, 0.63)		0.80
Insulin use, U/kg/day			
LS mean change (SE) from baseline at Week 52	0.07 (0.03)	0.24 (0.04)	
Difference for golimumab vs placebo (95% CI)	–0.18 (–0.27, –0.08)		0.001
Mean (SD) hypoglycemic events† from baseline to Week 52	38 (36)	43 (34)	
Rate ratio (95% CI)	0.90 (0.63, 1.29)		0.8

In participants <18 years of age, a post hoc analysis showed a 36% reduction in ADA Level 2 hypoglycemic events (BG <54 mg/dL).

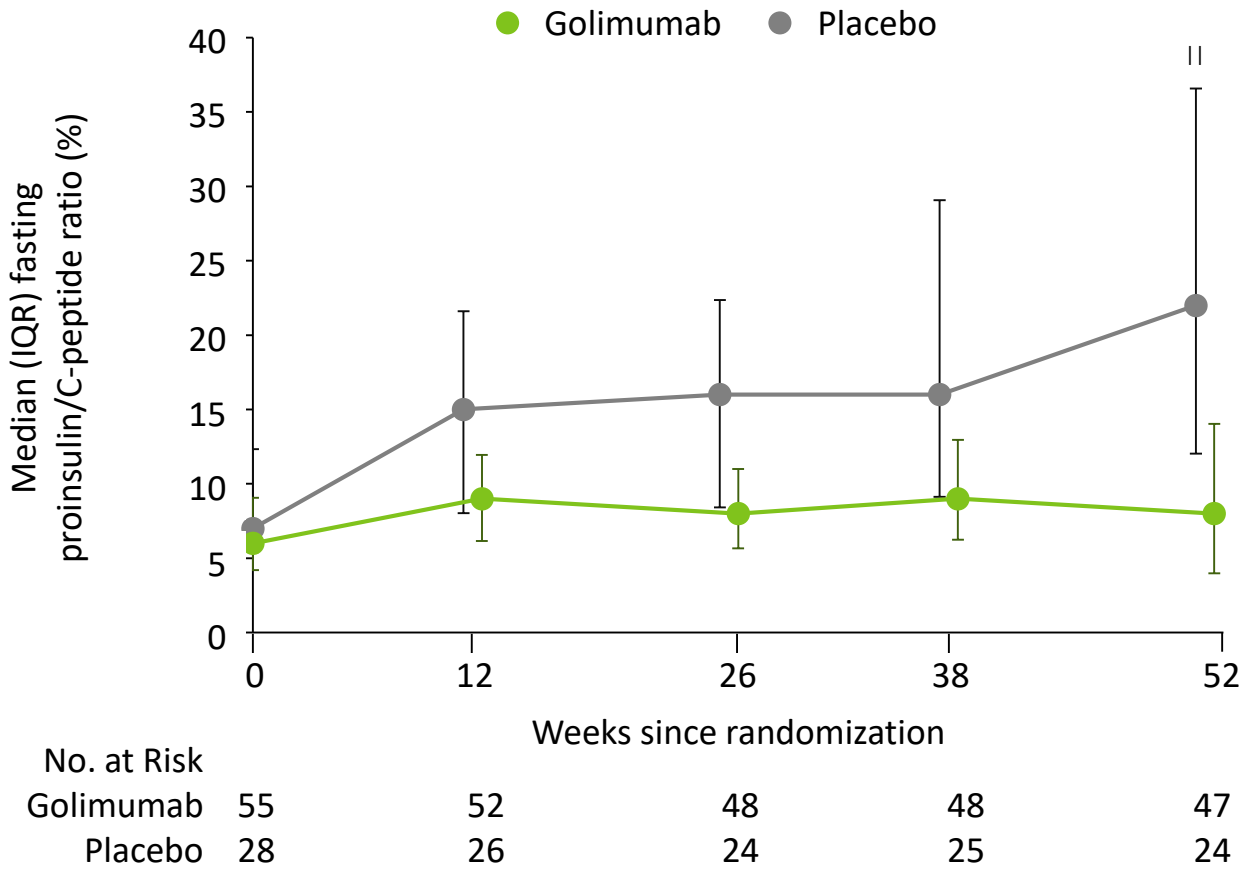
LS, least squares; SE, standard error.
*Hochberg approach is applied within secondary endpoint analyses.
†Defined as biochemically confirmed BG ≤70 mg/dL irrespective of symptoms and all events of severe hypoglycemia.

Additional Prespecified Analyses

Proportion of Responders by Treatment



Fasting Proinsulin/C-peptide Ratio§



IQR, interquartile ratio.
*Defined as having an increase or minimal decrease in C-peptide AUC ≤5% from baseline.
†Defined as having an insulin dose-adjusted A1c remission score ≤9 at Week 52.
‡Defined as meeting criteria for both C-peptide and partial remission responders.

§The C-peptide and proinsulin levels were assessed at Northwest Lipid Metabolism and Diabetes Research Laboratory (Seattle, WA) using 2-site immuno-enzymometric assays and radioimmunoassay kits (Millipore Inc.), respectively.
||At Week 52, the 95% Hodges-Lehmann CI of median difference = (0.064, 0.184).

Adverse Events

	Golimumab (n = 56)	Placebo (n = 28)
≥1 AE	91%	82%
≥1 serious AE*	2%	4%
≥1 AE leading to discontinuation	4%	0%
≥1 AE related to study drug	43%	43%
≥1 infection	71%	61%
Serious infection	0%	0%
Hypoglycemia	23%	7%
Diabetic ketoacidosis	0%	0%
≥1 injection site reaction	23%	29%
New or worsening autoimmune disease	0%	4%

- Hypoglycemic events were reported as AEs at the investigator's discretion. Seven of the 13 golimumab hypoglycemia AEs were from a single site reporting hypoglycemia AEs in all participants (including 2 in the placebo group); the other 6 hypoglycemia AEs were from 5 different sites

AE, adverse event.
*One serious AE was reported in each treatment group; neither was related to study treatment nor led to study or study drug discontinuation.

Conclusions

- In this phase 2a study in children and young adults with newly diagnosed stage 3 T1D, golimumab preserved endogenous insulin production and reduced exogenous insulin requirements
- Both groups had good treat-to-target glycemic control, and the change from baseline in HbA1c did not differ significantly between groups
- In a post hoc analysis, ADA Level 2 hypoglycemic episodes (BG <54 mg/dL) were lower in the pediatric population
- Compared to placebo, the golimumab group had a higher percentage of participants with C-peptide increase or minimal loss and were in partial remission while experiencing little or no increase in proinsulin/C-peptide ratio over time. These findings suggest that golimumab may be arresting disease progression for a large subset of patients
- This study used a novel T1D-specific dosing regimen for golimumab, which had a favorable safety profile consistent with regimens used previously, without any serious infections in either group
- These results support golimumab as a potential disease-modifying therapy for T1D