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LETTER TO THE EDITOR

Immunogenicity and pharmacokinetics of guselkumab among patients with moderate-to-severe psoriasis in VOYAGE-1 and VOYAGE-2

Dear Editor,

Development of anti-drug antibodies (ADA) to biologic agents may impact the effectiveness and/or safety of psoriasis treatment.[1–3] As several factors can influence development (e.g. molecular structure, dosing regimen) or clinical impact (e.g. neutralising antibodies [NAb]) of ADA,[4–8] the ability to predict the immunogenicity of any particular biologic is limited. Thus, evaluating the clinical significance of ADA over time is informative. Here, 5-year data from two large Phase 3, randomized studies (VOYAGE-1 and VOYAGE-2) were assessed for long-term presence and clinical impact of ADA to guselkumab, a fully human IgG1λ monoclonal antibody that binds the p19 subunit of interleukin-23.

In VOYAGE-1 and VOYAGE-2, guselkumab demonstrated superior efficacy to placebo and adalimumab with a favourable safety profile in adults with moderate-to-severe plaque psoriasis.[9,10] In both studies, patients randomized to placebo or adalimumab switched to guselkumab by Week (W)76, at the latest, and continued receiving guselkumab through W252. Overall, 774/837 patients in VOYAGE-1 and 947/992 in VOYAGE-2 received guselkumab. Guselkumab ADA were detected using a validated, drug-tolerant electrochemiluminescence immunoassay (ECLIA) method (Meso Scale Discovery). Among guselkumab-treated patients with evaluable ADA samples, 111/770 (14.4%) and 146/943 (15.5%) patients in VOYAGE-1 and VOYAGE-2, respectively, were ADA-positive at some point through W264; 82.0% had peak titres ≤1:160. In VOYAGE-1, among guselkumab-treated patients with evaluable ADA samples, 16.1% of patients who continued guselkumab through W252 were ADA-positive versus 7.4% of those who discontinued/withdrew before W252; corresponding values for VOYAGE-2 were 15.8% and 14.4%. Higher ADA titres were not observed among patients who discontinued guselkumab. Only 5 (4.5%) and 8 (5.5%) ADA-positive patients in VOYAGE-1 and VOYAGE-2, respectively, had NAb to guselkumab (defined as ≥22.46% inhibition of ECLIA signal versus controls), equivalent to 0.76% of guselkumab-treated patients with ADA-evaluable samples across studies.

Through W264, serum guselkumab concentrations were comparable between ADA-positive and ADA-negative patients (Figure 1), indicating no discernible impact of ADA on guselkumab pharmacokinetics. However, most patients had low ADA titres, limiting the ability to evaluate the effect of high titres on guselkumab concentrations.

Development of guselkumab ADA did not appear to impact clinical response, nor did titre levels. In both studies, ≥80% and ≥50% of patients achieved nearly clear skin (Psoriasis Area and Severity Index [PASI]90 or Investigator's Global Assessment [IGA]0/1) and clear skin (PASI100 or IGA0), respectively, regardless of ADA status (Table 1). Among the 13 NAb-positive patients, 8/11 patients with evaluable efficacy data at W252 had clear skin. Due to the limited number of patients with ADA titres ≥1000 or NAb, these observations should be interpreted cautiously.

Injection site reactions (ISRs) occurred in 8.1% of ADA-positive and 5.0% of ADA-negative patients in VOYAGE-1; corresponding values in VOYAGE-2 were 10.3% and 5.1%. These data should also be interpreted cautiously due to the limited number of patients with ADA and/or ISRs throughout the study. No serious ISRs occurred. In VOYAGE-2, 1 ADA-positive patient discontinued treatment due to an ISR (severe granuloma that resolved) and 1 NAb-positive patient experienced a mild ISR (injection-site hematoma) after developing NAb.

As several factors contribute to ADA development, cross-study or cross-biologic comparisons of ADA within the literature are highly confounded. However, to provide a practical framework for considering risks associated with ADA, Tsakok et al proposed categorising biologic psoriasis treatments into three broad classes: higher risk, lower risk, or no established risk.[8] Along with brodalumab, etanercept, and secukinumab, guselkumab was classified as "no established risk to date" based on data through up to 2 years of guselkumab treatment. The data presented here demonstrate that development of guselkumab ADA had no clinically relevant impact after up to 5 years of guselkumab exposure.

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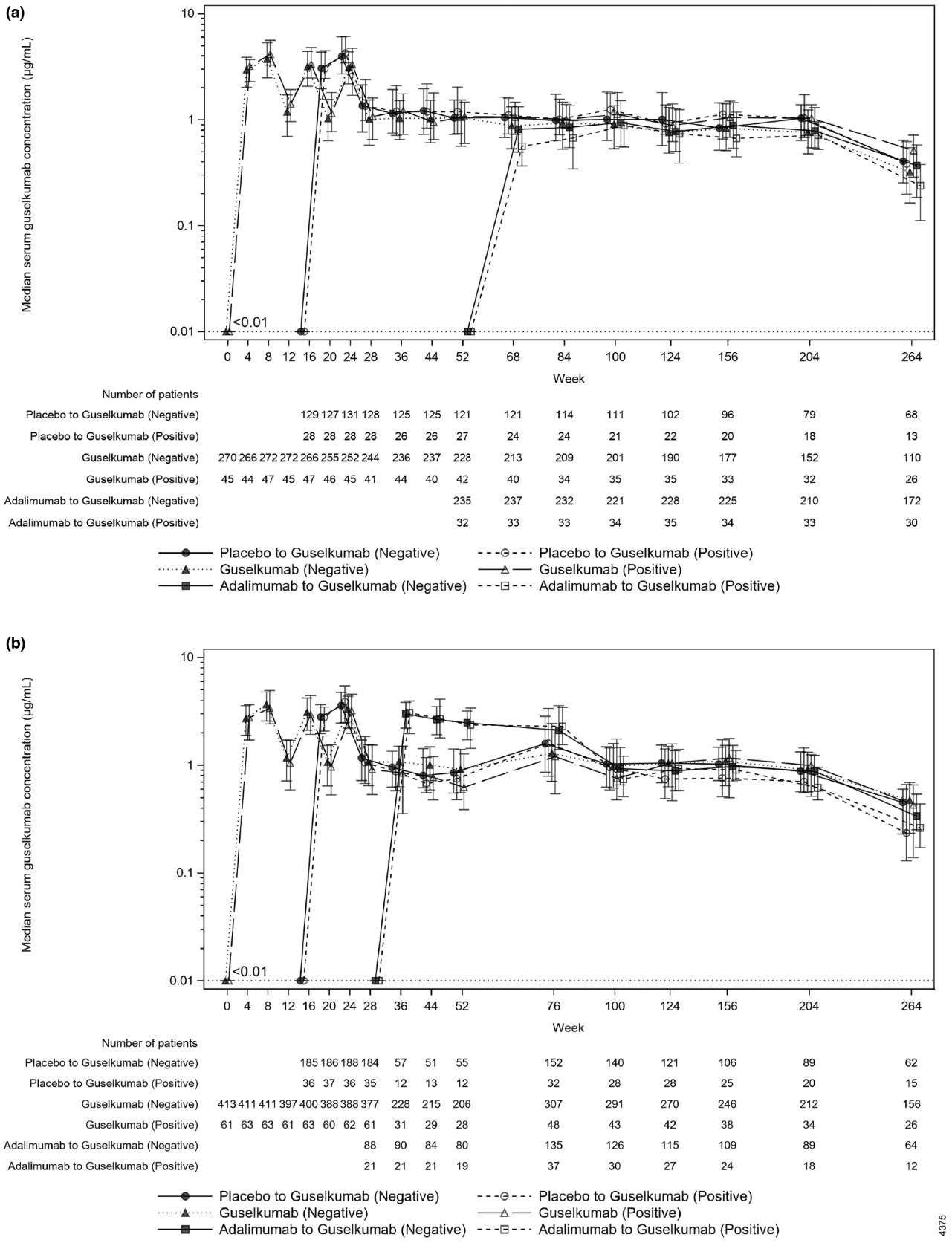

FIGURE 1 Median (IQR) serum guselkumab concentration through Week 264 by treatment group at randomisation and by ADA status in VOYAGE-1 (a) and VOYAGE-2 (b). Serum guselkumab concentrations were quantified using an ECLIA capable of detecting free and ADA-bound guselkumab (lowest quantifiable concentration 0.01 µg/mL). Abbreviations: ECLIA, electrochemiluminescence immunoassay; IQR, interquartile range.

TABLE 1 Clinical response at Week 252 by ADA status through Week 264 among guselkumab-treated patients with evaluable immunogenicity samples.[a]

			Peak titres for ADA-positive patients			
	Negative[b]	Positive[c]	10	>10 to <100	≥100 to <1000	≥1000
VOYAGE-1						
Guselkumab-treated patients with evaluable samples and available efficacy data,[a] *n*	536	101	31	43	18	9
PASI response,[d] *n* (%)						
PASI 100	280 (52.2)	57 (56.4)	19 (61.3)	21 (48.8)	10 (55.6)	7 (77.8)
PASI 90	445 (83.0)	87 (86.1)	25 (80.6)	39 (90.7)	15 (83.3)	8 (88.9)
PASI ≥75% to <90%	54 (10.1)	10 (9.9)	5 (16.1)	4 (9.3)	0	1 (11.1)
PASI ≥50% to <75%	20 (3.7)	3 (3.0)	1 (3.2)	0	2 (11.1)	0
PASI <50%	17 (3.2)	1 (1.0)	0	0	1 (5.6)	0
IGA score,[d] *n* (%)						
IGA 0	292 (54.5)	58 (57.4)	19 (61.3)	22 (51.2)	10 (55.6)	7 (77.8)
IGA 0/1	437 (81.5)	89 (88.1)	27 (87.1)	39 (90.7)	15 (83.3)	8 (88.9)
IGA ≥2	99 (18.5)	12 (11.9)	4 (12.9)	4 (9.3)	3 (16.7)	1 (11.1)
VOYAGE-2						
Guselkumab-treated patients with evaluable samples and available efficacy data,[a] *n*	619	117	42	41	27	7
PASI response,[d] *n* (%)						
PASI 100	323 (52.2)	67 (57.3)	21 (50.0)	24 (58.5)	16 (59.3)	6 (85.7)
PASI 90	505 (81.7)	94 (80.3)	32 (76.2)	34 (82.9)	22 (81.5)	6 (85.7)
PASI ≥75% to <90%	74 (12.0)	14 (12.0)	7 (16.7)	3 (7.3)	4 (14.8)	0
PASI ≥50% to <75%	18 (2.9)	4 (3.4)	0	2 (4.9)	1 (3.7)	1 (14.3)
PASI <50%	22 (3.6)	5 (4.3)	3 (7.1)	2 (4.9)	0	0
IGA score,[d] *n* (%)						
IGA 0[e]	337 (54.5)	70 (59.8)	22 (52.4)	26 (63.4)	16 (59.3)	6 (85.7)
IGA 0/1[e]	527 (85.3)	95 (81.2)	33 (78.6)	32 (78.0)	24 (88.9)	6 (85.7)
IGA ≥2[e]	91 (14.7)	22 (18.8)	9 (21.4)	9 (22.0)	3 (11.1)	1 (14.3)

Abbreviations: ADA, anti-drug antibodies; IGA, Investigator's Global Assessment; PASI, Psoriasis Area and Severity Index.

[a]Includes patients who received ≥1 dose of guselkumab, including those who crossed over from placebo or adalimumab. As validated, the sensitivity threshold for ADA to guselkumab was 15 ng/mL in the presence of up to 3125 ng/mL of guselkumab in human serum samples.

[b]Includes all patients whose last sample was negative and excludes patients who were positive for antibodies to guselkumab through Week 264.

[c]Includes patients who had ≥1 positive sample at any time after their first guselkumab administration through Week 264.

[d]Includes patients who had ≥1 evaluable sample after their first guselkumab administration and for whom efficacy assessments at Week 252 were performed.

[e]IGA results were not available for 1 patient in VOYAGE 2 (*N* = 618).

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CONFLICT OF INTEREST STATEMENT

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DATA AVAILABILITY STATEMENT

The data sharing policy of Janssen Pharmaceutical Companies of Johnson & Johnson is available at https://www.janssen.com/clinical-trials/transparency. As notes on this site, requests for access to the study data can be submitted through Yale Open Data Access Project site at https://yoda.yale.edu.

A. Armstrong[1]
K. Eyerich[2]
C. Conrad[3]
Y. Zhu[4]
Y.-W. Yang[5]
M. Miller[4]
Y. You[4]
Y.-K. Shen[4]
P. Foley[6]
C. E. M. Griffiths[7,8]
B. Strober[9,10]

[1]*Keck School of Medicine, University of Southern California, Los Angeles, California, USA*
[2]*University of Freiburg, Baden-Württemberg, Germany*
[3]*Lausanne University Hospital CHUV, Lausanne, Switzerland*
[4]*Janssen Research & Development, LLC, Spring House, Pennsylvania, USA*
[5]*Immunology Global Medical Affairs, Janssen Pharmaceutical Companies of Johnson & Johnson, Horsham, Pennsylvania, USA*
[6]*The University of Melbourne, St. Vincent's Hospital Melbourne and Probity Medical Research, Skin Health Institute, Carlton, Victoria, Australia*
[7]*Dermatology Centre, NIHR Manchester Biomedical Research Centre, University of Manchester, Manchester, UK*
[8]*King's College Hospital, King's College London, London, UK*
[9]*Yale University, New Haven, Connecticut, USA*
[10]*Central Connecticut Dermatology Research, Cromwell, Connecticut, USA*

Correspondence
Bruce Strober, Central Connecticut Dermatology Research, 1 Willowbrook Rd, Cromwell, CT 06416, USA.
Email: brucestrober30@me.com

ORCID

K. Eyerich https://orcid.org/0000-0003-0094-2674
C. Conrad https://orcid.org/0000-0002-2547-3440
C. E. M. Griffiths https://orcid.org/0000-0001-5371-4427
B. Strober https://orcid.org/0000-0002-8394-2057

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