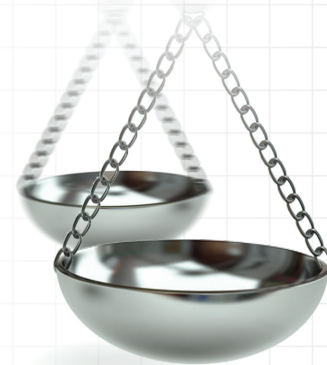




Letter to the Editor: Matching-adjusted indirect comparison between garadacimab and lanadelumab for the long-term prophylactic treatment of patients with hereditary angioedema

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We read with interest the recent article titled “Matching-adjusted indirect comparison between garadacimab and lanadelumab for the long-term prophylactic treatment of patients with hereditary angioedema” [1]. While indirect treatment comparisons such as matching-adjusted indirect comparisons (MAICs) provide valuable evidence in the absence of head-to-head clinical trials, the robustness of findings depends on adherence to core methodological principles of the comparison. We have identified several areas where we believe these methodological requirements may not be fully met, potentially affecting the validity of the conclusions, and we identify other aspects that limit the relevance of the findings to clinical practice.

Walsh *et al.* compared five outcomes relating to efficacy and quality of life (QoL) between garadacimab (200 mg once monthly) and two lanadelumab dosing intervals (300 mg every 2 weeks [Q2W] or every 4 weeks [Q4W]) as long-term prophylaxis in patients aged ≥ 12 years with hereditary angioedema (HAE) [1]. The MAIC used data from participants enrolled in the 6-month Phase III VANGUARD Study [2] and a 12-week Phase II study [3] of garadacimab (with data pooled across both), and from participants enrolled in the 6-month Phase III HELP Study [4] of lanadelumab. First, we wish to explain that because of fundamental differences between the HELP Study and the real-world use of the Q4W regimen, the indirect comparison between garadacimab and lanadelumab Q4W has limited clinical relevance. We highlight this because, for the primary end point (time-normalized number of HAE attacks), the authors found no difference between garadacimab and lanadelumab Q2W, but reported a statistically significant improvement with garadacimab compared with lanadelumab Q4W.

At initiation of the HELP Study [4], participants were randomly assigned to receive lanadelumab 150 mg Q4W, lanadelumab 300 mg Q2W, lanadelumab 300 mg Q4W or placebo. There were no patients who initiated lanadelumab 300 mg on a Q2W regimen and moved to Q4W. All three lanadelumab regimens resulted in significant reductions in HAE attack rates versus placebo, with the 300 mg Q2W regimen resulting in the numerically largest reduction. Thus, lanadelumab was approved with a starting dose of 300 mg Q2W with a dose-interval extension to 300 mg Q4W allowed in patients who are ‘stably attack free’ or ‘well controlled (e.g., attack free)’ on Q2W dosing [5,6]. Consequently, efficacy and QoL outcomes in study participants randomized directly to lanadelumab Q4W in HELP likely do not reflect outcomes in patients treated with lanadelumab Q4W in clinical practice, who have started on Q2W dosing. Indeed, the independent Expert Advisory Group of the UK National Institute for Health and Care Excellence (NICE) stated it is appropriate to consider equal efficacy between lanadelumab 300 mg Q4W and Q2W in clinical practice [7], rather than use Q4W data from HELP, which shows a numerically smaller attack rate reduction versus the Q2W regimen. In summary, lanadelumab 300 mg Q4W outcome data from HELP do not provide an appropriate substitute for real-world Q4W outcomes, undermining the validity of the indirect

comparison between garadacimab and lanadelumab 300 mg Q4W described by Walsh *et al.* Therefore, for the remainder of our commentary, we will focus on the results and interpretation of the indirect comparison between garadacimab and lanadelumab Q2W.

MAICs use individual patient-level data from the trial(s) of one treatment to match the aggregated baseline characteristics of patients in the trial(s) of another treatment by weighting individual patient data based on treatment effect modifiers [8]. Bodies such as the NICE Decision Support Unit have developed best practices for MAIC reporting, including presentation of the distribution of weights (and reporting the number of individuals assigned zero weight) [9]. However, this is not reported by Walsh *et al.*, limiting the understanding of the calculation of the effective sample size.

Although other types of heterogeneity remain, the goal of a MAIC is to balance the heterogeneity between different study populations. The garadacimab Phase II study did not include any patients in the 12 to <18 age group. Methodologically, while the MAIC matched the VANGUARD and HELP study populations according to the proportions of patients aged <40 years, this approach was not consistent with the more sophisticated matching using categories of 12 to <18, 18 to <40, 40 to <65 and ≥ 65 years conducted in the recent MAIC of garadacimab and donidalorsen conducted by the same author group [10]. Inconsistency in approaches raises questions. The primary HELP publication provided the age distributions of 12 to <18, 18 to <65, and ≥ 65 years [4], and the subgroup analysis further provided the 18 to <40 and 40 to <65-years distributions [11]. Using more detailed categorization, particularly both 12 to <18 and 18 to <40-years age groups, would have provided more comparable populations, particularly given different trial age eligibility criteria in the garadacimab Phase II study.

The rationale for the authors' inclusion of the 12-week Phase II garadacimab study and pooling data with those from the Phase III VANGUARD study is unclear, beyond increasing the initial sample size to mitigate reductions in the effective sample size after adjusting for effect modifiers. Pooling garadacimab data from 12-week and 26-week trials inevitably introduces unnecessary heterogeneity when making a comparison with the exclusively 26-week data from the lanadelumab study. Calculations by Walsh and colleagues would have benefitted substantially from a sensitivity analysis based on a MAIC including only Phase III data.

After weighting the garadacimab pooled Phase II and III data to match the HELP Study population characteristics for age <40 years, sex, body weight <75 kg and HAE attack rate during run-in, Walsh *et al.* reported no statistical differences between garadacimab and lanadelumab Q2W for the primary outcome of time-normalized number of HAE attacks [1]. The MAIC also showed no significant differences between garadacimab and lanadelumab Q2W for the outcomes of time-normalized number of HAE attacks that required on-demand treatment or proportion of attack-free patients over the trial period. Of note, assumptions, and reliance upon them, differ between anchored and unanchored comparisons when trial follow-up is not the same. In the unanchored case, used for the proportion of attack-free patients and where there is no 'placebo-anchoring', the differences between the studies are assumed to affect both the treatment and the anchor arm similarly, preserving the relative effect. In an unanchored analysis, differences between the arms that could impact outcomes are indistinguishable from the treatment effect. Traditional survival models resulting in calculation of hazard ratios can produce biased or uninterpretable results if the trial duration is too short to be consistent with longer follow-up. Importantly, the MAIC method requires assumption of proportional hazards [12], which is not necessarily valid for all time-to-event trials. This is particularly relevant in studying long-term prophylaxis because HAE is characterized by unpredictable attacks rather than a continuous disease state. For the binary end point of the proportion of attack-free patients, the authors generated simulated individual patient data for lanadelumab. A clearer justification for this, and details about simulation methodology, assumptions, distributions and covariates are not provided, introducing additional uncertainty and preventing independent validation.

Although the authors did report statistically significant differences in favor of garadacimab over lanadelumab Q2W in time-normalized number of moderate and/or severe HAE attacks and change in Angioedema QoL Questionnaire (AE-QoL), we believe there are fundamental issues with the analyses for both. In VANGUARD, with an attack that was categorized as mild, on-demand medication to treat the attack may not have been necessary, but was not prohibited according to the definition. Whereas, with a mild attack in the HELP Study (transient or with mild discomfort), no medical intervention/therapy was required. Therefore, an attack of the same severity could be classified as mild in VANGUARD but moderate in HELP. Furthermore, while the MAIC matched populations from VANGUARD to HELP with respect to age, sex, bodyweight and baseline attack rate, other critical treatment effect modifiers were not included. Overall, 16.5% of participants in the HELP Study had a medical history of depression and 13.8% had a history of anxiety [13], higher than rates for both in the garadacimab

trials, highlighting the importance of further population matching. Additionally, the participants in HELP had a mean baseline AE-QoL score of 43.8–48.8 [14] versus 38.8 [2] in garadacimab-treated patients in VANGUARD, indicating greater QoL impairment in participants enrolled in HELP. However, baseline AE-QoL was not included as a treatment effect modifier, potentially biasing the comparative AE-QoL conclusions. This is noteworthy as baseline AE-QoL scores have been found to be predictive of change in AE-QoL scores at Week 24 [15].

The authors state that garadacimab may provide improved therapeutic benefit compared with lanadelumab as long-term prophylaxis in patients with HAE. However, the 2025/2026 guidelines recommend both lanadelumab and garadacimab as first-line HAE LTP options and the general consensus is of equivalent effectiveness [16–19]. This reinforces the challenges in the clinical interpretation of indirect treatment comparisons in general. Given the methodological limitations raised, particularly the limited clinical relevance of lanadelumab Q4W comparisons, non-comparable treatment durations, outcome definition heterogeneity, missing adjustments for baseline QoL, and use of simulated data without transparency, we feel that it may be misleading to summarise the MAIC as showing ‘improved efficacy and QoL with garadacimab compared with lanadelumab across multiple end points’. The validity of comparative effectiveness conclusions, especially for secondary outcomes, has substantial uncertainty and should be interpreted with appropriate caution.

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Competing interests disclosure

I Andresen is an employee of Takeda Pharmaceuticals International AG, and holds stock/options in Takeda Pharmaceutical Company Limited. N Khutoryansky is an employee of Cytel, contracted by Takeda Development Center Americas, Inc. SL Feeny is an employee of Ampersand Medical, contracted by Takeda Development Center Americas, Inc. A Dangel is an employee of Takeda Pharmaceuticals USA, Inc., and holds stock/options in Takeda Pharmaceutical Company Limited. The authors have no other competing interests or relevant affiliations with any organization or entity with the subject matter or materials discussed in the manuscript apart from those disclosed.

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Under the direction of the authors, Jon Waldron, PhD, employee of Envision Catalyst, an Envision Medical Communications agency, a part of Envision Pharma Group, provided medical writing assistance, funded by Takeda Development Center Americas, Inc.

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References

- Walsh S, Haltner A, Bartlett M *et al*. Matching-adjusted indirect comparison between garadacimab and lanadelumab for the long-term prophylactic treatment of patients with hereditary angioedema. *J. Comp. Eff. Res.* 14(8), e240237 (2025).
- Craig TJ, Reshef A, Li HH *et al*. Efficacy and safety of garadacimab, a factor XIIa inhibitor for hereditary angioedema prevention (VANGUARD): a global, multicentre, randomised, double-blind, placebo-controlled, Phase III trial. *Lancet* 401, 1079–1090 (2023).
- Craig T, Magerl M, Levy DS *et al*. Prophylactic use of an anti-activated factor XII monoclonal antibody, garadacimab, for patients with C1-esterase inhibitor-deficient hereditary angioedema: a randomised, double-blind, placebo-controlled, Phase II trial. *Lancet* 399, 945–955 (2022).
- Banerji A, Riedl MA, Bernstein JA *et al*. Effect of lanadelumab compared with placebo on prevention of hereditary angioedema attacks: a randomized clinical trial. *JAMA* 320, 2108–2121 (2018).
- Takeda Pharmaceutical Company Limited. Takhzyro highlights of Prescribing Information 2022. https://www.accessdata.fda.gov/drugsatfda_docs/label/2022/761090s003lbl.pdf
- Takeda Pharmaceuticals International AG. Takhzyro (INN-lanadelumab) summary of product characteristics 2023. https://www.ema.europa.eu/en/documents/product-information/takhzyro-epar-product-information_en.pdf

7. National Institute for Health and Care Excellence (NICE). Garadacimab for preventing recurrent attacks of hereditary angioedema in people 12 years and over 2025. <https://www.nice.org.uk/guidance/ta1101>
8. Signorovitch JE, Sikirica V, Erder MH *et al*. Matching-adjusted indirect comparisons: a new tool for timely comparative effectiveness research. *Value Health* 15, 940–947 (2012).
9. The National Institute for Health and Care Excellence Decision Support Unit. NICE DSU Technical Support Document 18: methods for population-adjusted indirect comparisons in submissions to NICE 2016. <https://sheffield.ac.uk/nice-dsu/tsds/population-adjusted>
10. Samjoo IA, Walsh S, Haltner A *et al*. Matching-adjusted indirect comparison between garadacimab and donidalorsen for long-term prophylaxis in hereditary angioedema. Presented at: *ISPOR Europe 2025*, Glasgow, UK (9–12 November 2025). https://www.ispor.org/docs/default-source/cti-meeting-21305-documents/1a5ea685-925a-4858-9b4e-65e06f65a7a3.pdf?sfvrsn=b225dcb8_0
11. Johnston DT, Busse PJ, Riedl MA *et al*. Effectiveness of lanadelumab for preventing hereditary angioedema attacks: subgroup analyses from the HELP study. *Clin. Exp. Allergy* 51, 1391–1395 (2021).
12. Woods BS, Hawkins N, Scott DA. Network meta-analysis on the log-hazard scale, combining count and hazard ratio statistics accounting for multi-arm trials: a tutorial. *BMC Med. Res. Methodol.* 10, 54 (2010).
13. Lumry WR, Maurer M, Weller K *et al*. Long-term lanadelumab treatment improves health-related quality of life in patients with hereditary angioedema. *Ann. Allergy Asthma Immunol.* 131, 101–108; e3 (2023).
14. Lumry WR, Weller K, Magerl M *et al*. Impact of lanadelumab on health-related quality of life in patients with hereditary angioedema in the HELP study. *Allergy* 76, 1188–1198 (2021).
15. Craig T, Yarlus A, Keeney T *et al*. Predictors of disease control, attack rate, and quality of life in HAE: an exploratory analysis. *J. Allergy Clin. Immunol.* 157, AB53 (2026).
16. Pharmaceutical Benefits Advisory Committee. Garadacimab, injection 200 mg in 1.2 ml pre-filled pen, TBD, CSL Behring (Australia) Pty Ltd 2025. <https://www.pbs.gov.au/info/industry/listing/elements/pbac-meetings/psd/2024-11/garadacimab-PSD-November-2024>
17. Agencia Española De Medicamentos y Productos Sanitarios. Informe de Posicionamiento Terapéutico de garadacimab (Andembry®) en la prevención rutinaria de las crisis recurrentes de angioedema hereditario en pacientes adultos y adolescentes a partir de 12 años de edad 2025. <https://www.aemps.gob.es/medicamentosUsoHumano/informesPublicos/docs/2025/IPT-406-Andembry-garadacimab.pdf>
18. Betschel S, Binkley K, Borici-Mazi R *et al*. The International/Canadian hereditary angioedema guideline. *Allergy Asthma Clin. Immunol.* 22(1), 24 (2026).
19. Vázquez DO, Giavina-Bianchi P, Josviack D *et al*. The 2025 WAO Guidelines for the classification, diagnosis, and treatment of hereditary angioedema, with consideration of worldwide disparities. *World Allergy Organ. J.* 19(5), 101335 (2026).