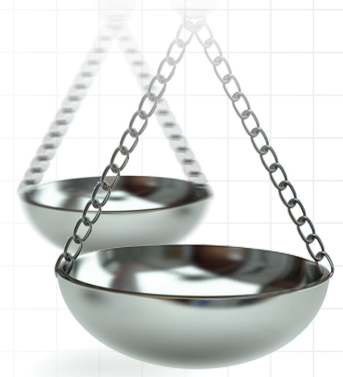




Response to Letter to the Editor regarding “Matching-adjusted indirect comparison between garadacimab and lanadelumab for the long-term prophylactic treatment of patients with hereditary angioedema”

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Following the letter to the editor concerning our article [1], we appreciate the opportunity to clarify the methodological rationale for the analysis and to address the interpretation of the findings. We respond below to the key issues raised.

Use of the lanadelumab 300 mg Q4W regimen

The present indirect treatment comparison (ITC) was designed to compare garadacimab with lanadelumab using the randomized evidence identified through a systematic literature review [1]. Randomized controlled trials remain the preferred source for ITCs because randomization minimizes bias and confounding. The only randomized evidence identified for lanadelumab 300 mg every 4 weeks (Q4W) was the HELP study, in which Q4W was evaluated as a starting randomized regimen. By contrast, the lanadelumab clinical program evidence for maintenance after stabilization is based on Q2W treatment in HELP-OLE (open-label extension) and was not eligible for inclusion in the systematic literature review as randomized comparative evidence [2].

We agree that interpretation of the Q4W comparison requires clinical context. Lanadelumab Q4W is not approved as a starting regimen; rather, labels and guidance describe dose-interval extension after patients are well controlled or stably attack-free on Q2W dosing [3–5]. We therefore do not suggest that HELP Q4W outcomes should be interpreted as fully generalizable to patients who initiate on Q2W and later extend their interval in clinical practice, nor do we consider equivalence between Q2W and Q4W maintenance regimens to have been established through robust randomized evidence. Accordingly, the Q4W results should be viewed as an analysis of the best available randomized evidence for that dosing interval, not as a direct representation of all real-world lanadelumab maintenance use. This caveat qualifies the clinical interpretation of the comparison, but does not invalidate the analysis itself, which transparently reflects the available randomized data.

Heterogeneity

Our approach was intended to balance reduction of heterogeneity with preservation of a representative and analytically robust study population. More granular age categories were explored during development of the analysis; however, at the time, use of finer categories raised data-anonymization constraints that would have required exclusion of a substantial number of garadacimab subjects from the individual patient data (IPD). This

would have reduced representativeness before matching and introduced a different potential source of bias. As data access conditions and anonymization requirements evolved, more granular age categories could be used in a subsequent MAIC of garadacimab and donidalorsen without materially compromising the underlying IPD [6]. We therefore view the different age specifications as an evolution in feasible data handling rather than a methodological inconsistency.

Pooling the Phase II and Phase III garadacimab data was prespecified and clinically motivated. It was consistent with the approach adopted in a published network meta-analysis in this therapeutic area [7], and in a rare disease such as hereditary angioedema (HAE) it helped preserve statistical information and effective sample size (ESS) after weighting. Although pooling trials with different durations can introduce additional heterogeneity, this limitation was balanced against the benefit of a larger, more stable analytic population. Clinical assessment prior to pooling found the studies sufficiently similar in design, eligibility criteria, baseline characteristics and outcome assessment to support the comparison, and differences in follow-up were addressed through time offsets in the models [8]. Sensitivity analyses excluding the Phase II study were performed. Relative to the pooled analysis, ESS was reduced by approximately 10–57% and confidence intervals widened, supporting the pooling of the Phase II and Phase III garadacimab data. Treatment effect estimates were generally directionally consistent with the primary analysis, and the proportion of attack-free patients versus lanadelumab Q4W remained statistically significant.

We also acknowledge that minor differences between HELP and VANGUARD in definitions of mild and moderate attacks may contribute to residual heterogeneity. The VANGUARD mild definition allowed ‘other concomitant medications’ to relieve angioedema symptoms, but did not explicitly state that HAE rescue/on-demand medication use was compatible with mild severity. Such ambiguity is not uncommon when synthesizing data from independently conducted trials and does not, in itself, invalidate an analysis [9]. Across both studies, the central discriminator of severity was functional impact and/or need for assistance, with medication use serving as a supporting criterion. Therefore, attacks with meaningful functional impairment would be expected to be categorized as moderate or severe in both trials. Most importantly, severity was assessed using the same criteria across treatment arms within each trial, supporting the internal validity of within-trial treatment effects estimated by the MAIC. Finally, current guidelines recommend that all HAE attacks be considered for on-demand treatment and that attacks be treated as early as possible, regardless of severity [10,11]. This broader clinical principle should be considered when interpreting end points based on attack severity or on-demand treatment use.

Weighting & modeling

Effective sample size was reported as the primary summary measure of the impact of weighting on the garadacimab IPD, consistent with common MAIC reporting practice. We also agree that additional descriptive summaries of the weight distribution would provide complementary diagnostic information regarding the stability and concentration of the weights. However, for the attack-related efficacy outcomes, the relatively limited reductions in ESS (4–30%) suggest that weighting preserved a substantial proportion of the available information and are not indicative of severe weight concentration. Consistent with this, the weights were generally centered around 1.0 and showed no evidence of extreme weighting across the MAICs for the efficacy outcomes. Together, these findings suggest that the matching was unlikely to have relied on a small subset of heavily weighted patients or to have effectively excluded a meaningful proportion of patients through assignment of near-zero weights. Larger reductions in ESS were observed for the AE-QoL analyses (49–55%), reflecting a greater loss of information following weighting. This primarily reflects the more restricted analysis population, as AE-QoL outcome was unavailable from the Phase II study and 11 patients in the Phase III had missing AE-QoL data, resulting in greater baseline imbalance between studies, particularly with respect to run-in attack rate.

To account for different follow-up durations in the attack-free end point, the model used a weighted generalized linear model with a binomial likelihood, a complementary log-log link, and an offset for the logarithm of follow-up time [8]. The trial-level HELP attack-free proportions reported by Banerji *et al.* were reconstructed as simulated patient-level records solely to allow the binomial model to be fitted in the same data structure as the weighted garadacimab IPD [12]. Each reconstructed HELP record was assigned 182 days of follow-up and a weight of 1. No additional patient characteristics were imputed for HELP beyond what was required to reproduce the published aggregate attack-free proportions. We acknowledge that the complementary log-log model has a hazard-based interpretation and relies on assumptions that should be considered when interpreting the result; however, the model explicitly accounts for follow-up duration and was selected because it is appropriate for a binary end point observed across differing follow-up times.

Selection of treatment effect modifiers

Our analysis applied a consistent, pre-specified set of treatment effect modifiers across end points, informed by clinical expert consultation. Baseline AE-QoL was not included in this set, it was therefore not adjusted for in the AE-QoL MAIC. Because AE-QoL was analyzed as change from baseline, baseline differences are partially accounted for by the outcome definition. We nevertheless acknowledge that residual influence of baseline AE-QoL on comparative change-from-baseline estimates cannot be excluded, particularly in light of the correspondents’ cited research, which post-dated our analysis. This is a reasonable limitation and should be considered in future ITCs that include QoL outcomes.

As stated in the original manuscript, histories of anxiety and depression were ranked by clinical experts as important covariates but were not reported in the primary HELP publication and therefore could not be adjusted for. The cited estimates derive from a subsequent HELP-OLE report rather than the randomized HELP population and include rollover patients across the lanadelumab program, including a 150 mg Q4W regimen not relevant to the comparison [13]. We acknowledge that unmeasured effect modifiers remain a limitation of any MAIC, but we consider it unlikely that these unadjusted covariates would materially alter the overall direction of findings.

Framing of the study conclusions

We respectfully maintain that the study conclusions were framed appropriately and transparently. The manuscript discussed key limitations, including residual heterogeneity, reliance on comparator-reported covariates, the constraints of ITCs, and the absence of head-to-head evidence. Within these limitations, the direction of estimated effects was consistently in favor of garadacimab across evaluated outcomes, with statistical significance for several end points. The manuscript deliberately used qualified language, stating that garadacimab ‘may’ provide improved therapeutic benefit, to reflect the uncertainty inherent to ITC methodology.

We agree that guideline recommendations listing both garadacimab and lanadelumab among current first-line long-term prophylaxis options should be interpreted alongside [11,14–16], not in opposition to, comparative effectiveness analyses. Guidelines identify clinically appropriate treatment options for broad use, whereas ITCs seek to quantify relative efficacy where direct head-to-head data are unavailable. The current evidence base should not be interpreted as proving equivalent efficacy between the two agents. Rather, additional evidence – including rigorously conducted ITCs, real-world evidence, and, where feasible, head-to-head studies – will be valuable to further differentiate treatments and support individualized decision-making for patients, clinicians, payers, and health technology assessment bodies.

In summary, our manuscript provides a rigorous synthesis of the available randomized evidence comparing garadacimab and lanadelumab in HAE, conducted according to NICE DSU best practice and supported by sensitivity/scenario analyses and related evidence in the therapeutic area [6,7,17]. In rare diseases, where head-to-head trials are challenging, carefully conducted ITCs provide decision-relevant evidence, provided they are interpreted with appropriate caution and in the context of the totality of available data and underlying methodological assumptions. We are grateful to the correspondents for their thoughtful critique, which has allowed us to further clarify these methodological and interpretive points.

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Author contributions

The authors were responsible for drafting or reviewing this response and for providing final approval. The authors meet the International Committee of Medical Journal Editors (ICMJE) criteria for authorship for this article, take responsibility for the integrity of the work, and have given approval for this version to be published.

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