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Matching-Adjusted Indirect Comparison Between Garadacimab and Donidalorsen for Long-Term Prophylaxis in Hereditary Angioedema

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BACKGROUND

- Hereditary angioedema (HAE) is a rare, potentially life-threatening condition characterized by recurrent episodes of swelling in various parts of the body, including the extremities, gastrointestinal tract, and airway. Long-term prophylaxis (LTP) is essential to achieve disease control and improve patients' quality of life.[1,2]
- Garadacimab, a monoclonal antibody targeting activated Factor XII (FXIIa), and donidalorsen, an antisense oligonucleotide targeting prekallikrein, have both demonstrated efficacy in separate Phase 3 randomized controlled trials (RCTs).[3,4]
- Garadacimab has been approved for use in LTP for HAE in Japan, Australia, the United Kingdom, European Union, Switzerland, Canada, and the United States.[5,6] Donidalorsen received approval for use in the United States.[7]
- In absence of head-to-head trials, we conducted a matching-adjusted indirect comparison (MAIC) to estimate the relative efficacy of garadacimab versus donidalorsen.

Objective

To estimate the relative efficacy of garadacimab 200 mg administered subcutaneously once monthly (GARA 200 QM) compared to donidalorsen 80 mg administered subcutaneously every four weeks (DONI 80 Q4W) and every eight weeks (DONI 80 Q8W) for LTP in patients with HAE.

Methods

MAICs were conducted using methods outlined by the NICE DSU TSD 18.[8,9]

Data sources:
- Individual patient data (IPD) were obtained from the Phase 3 VANGUARD trial (NCT04656418), which evaluated garadacimab.
- Published summary-level data were extracted from the Phase 3 OASIS-HAE trial (NCT05139810), which evaluated donidalorsen.

Covariate adjustment:
- To ensure comparability between the two trial populations, IPD from the VANGUARD trial were reweighted to match the baseline characteristics reported in the OASIS-HAE trial.
- The following clinically relevant treatment effect modifiers for adjustment were identified from the literature and clinical expertise and were ranked in order of importance by clinical experts.
  - HAE attack rate during the run-in period
  - Body mass index (BMI)
  - Age (12 to <18, 18 to <40, 40 to <65, ≥65 years)
  - Sex

Outcomes:
1. Time-normalized number of HAE attacks
2. Time-normalized number of moderate and/or severe HAE attacks
3. Proportion of attack-free patients

Base case analysis:
- Anchored MAICs were conducted for outcomes 1&2, which were reported relative to placebo in both trials.
  - Effect estimates for garadacimab vs placebo were derived using a weighted generalized linear model using a quasi-Poisson likelihood. Comparative efficacy estimates were expressed as rate ratios with corresponding 95% confidence intervals (CIs).
- For the proportion of attack-free patients, an unanchored MAIC was used due to zero events in the placebo arm of VANGUARD.
  - Comparative efficacy were estimated with hazard ratios and corresponding 95% CIs using a weighted binomial model with a complementary log-log link function and the logarithm of patient-level follow-up time as an offset.
- Treatment effect modifiers were adjusted for iteratively, until all four were adjusted in the base case analysis (indicated by red box).

Sensitivity analyses:
- Several sensitivity analyses were conducted to test the robustness of the findings. These included:
  - Pooling data from the Phase 2 and Phase 3 trials (VANGUARD & CSL312_2001 for garadacimab; OASIS-HAE & ISIS 721744-CS2 for donidalorsen).
  - Adjusting for race, in addition to prior modifiers, was included in addition to the base case analysis as it may influence treatment response.

Alternative analysis for proportion of attack-free patients:
- An alternative analysis was conducted for the proportion of attack-free patients outcome using a weighted binomial model with a complementary log-log link function and attack as the outcome.
  - The model estimated the probability of experiencing at least one attack, which was then converted back to the proportion of patients remaining attack-free and (reported as a relative risk) had total exposure been the same as observed in the OASIS-HAE study.
  - The hazard ratios from the base case analysis were converted to relative risks in the same way to allow for comparisons between the two approaches on the same scale.
- This methodology is more robust, as it aligns with standard time-to-event outcomes and avoids assuming more non-events with longer follow-up, and could substitute the base case for proportion of attack-free outcome.

Results

Base Case Analysis
- GARA 200 QM was associated with a statistically significant reduction in the time-normalized number of moderate and/or severe HAE attacks vs DONI 80 Q4W (rate ratio: 0.18; 0.06, 0.60; **Figure 1B**) and patients were statistically significantly twice as likely to be attack-free (hazard ratio: 2.21; 1.02, 4.79; **Figure 1C**).
- GARA 200 QM was associated with statistically significant reductions in both the time-normalized number of HAE attacks vs DONI 80 Q8W, (rate ratio : 0.21; 0.08, 0.54; **Figure 2A**) and time-normalized number of moderate and/or severe HAE attacks (rate ratio : 0.09; 0.03, 0.26; **Figure 2B**). Additionally, patients were statistically significantly three times as likely to be attack-free (hazard ratio : 3.02; 1.04, 8.79; **Figure 2C**).

Sensitivity Analyses
- Results of the sensitivity analyses were consistent with the base case analyses for each comparison in all outcomes, supporting the robustness of the methodology (**Table 1**).

Alternative Analysis for Proportion of Attack-free Patients
- The alternative analysis of attack-free patients yielded more robust results that are consistent with the results from base case analysis. GARA 200 QM was associated with a statistically significant increase in the likelihood of being attack-free vs DONI 80 Q4W (relative risk: 1.97; 1.14, 3.21 vs 1.80; 1.02, 2.87) and DONI 80 Q8W (relative risk: 2.54; 1.33, 5.59 vs 2.31; 1.04, 4.51) (**Table 2**).

Table 1: MAIC Results Summary[a] – GARA 200 QM vs. Comparator Treatment*

Treatment Effect	Outcome	Comparator Treatment	Base Case (Phase 3 only)[b]	Sensitivity (Pooled Phase 2 & 3)[c]	Sensitivity (Phase 3 only, additionally adjusting for race)[b]
Rate Ratio (95% CI)	Time-normalized number of HAE attacks [d]	DONI 80 Q4W	0.61 (0.21, 1.75)	0.63 (0.24, 1.67)	0.55 (0.20, 1.47)
		DONI 80 Q8W	**0.21 (0.08, 0.54)**	**0.17 (0.07, 0.43)[g]**	**0.19 (0.08, 0.47)**
	Time-normalized number of moderate and/or severe HAE attacks [e]	DONI 80 Q4W	**0.18 (0.06, 0.60)**	**0.25 (0.09, 0.68)**	**0.18 (0.05, 0.60)**
		DONI 80 Q8W	**0.09 (0.03, 0.26)**	**0.07 (0.02, 0.22)[g]**	**0.08 (0.03, 0.25)**
Hazard Ratio (95% CI)	Proportion of attack-free patients over the trial period [f]	DONI 80 Q4W	**2.21 (1.02, 4.79)**	**2.98 (1.53, 5.82)**	**2.28 (1.03, 5.05)**
		DONI 80 Q8W	**3.02 (1.04, 8.79)**	**4.13 (1.45, 11.72)[g]**	**3.23 (1.08, 9.69)**

Table 2: MAIC Alternative Analysis Results Summary[a] – GARA 200 QM vs. Comparator Treatment*

Treatment Effect	Outcome	Comparator Treatment	Base Case (Phase 3 only)[b]	Alternative Analysis
Relative Risk (95% CI)	Proportion of attack-free patients over the trial period [f]	DONI 80 Q4W	**1.80 (1.02, 2.87)**	**1.97 (1.14, 3.21)**
		DONI 80 Q8W	**2.31 (1.04, 4.51)**	**2.54 (1.33, 5.59)**

Statistically significant in favor of GARA 200 QM Numerically in favor of GARA 200 QM

Figure 1 (A,B,C): Base Case Analysis for GARA 200 QM vs. DONI 80 Q4W

Figure 1A: Time-normalized number of HAE attacks GARA 200 QM vs. DONI 80 Q4W

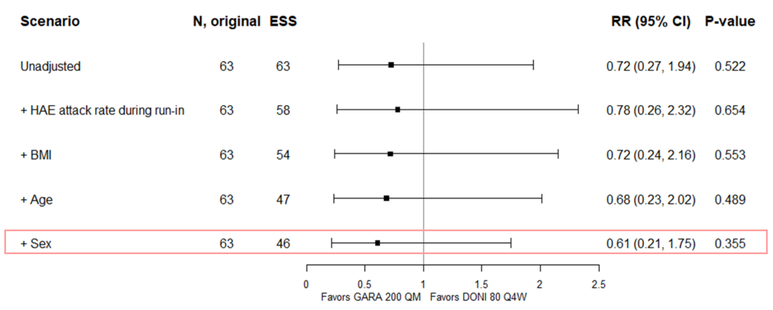


Figure 1B: Time-normalized number of moderate and/or severe HAE attacks GARA 200 QM vs. DONI 80 Q4W

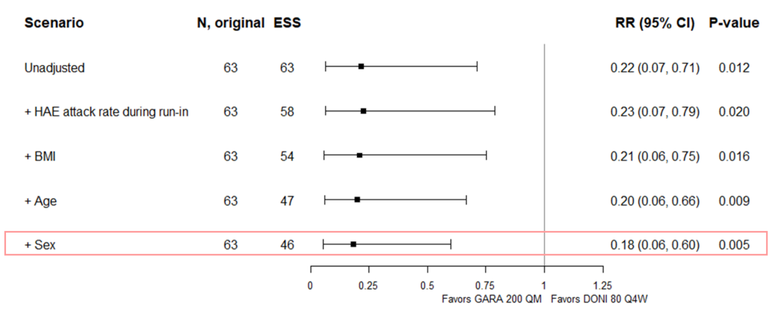


Figure 1C: Proportion of attack-free patients over the trial period GARA 200 QM vs. DONI 80 Q4W

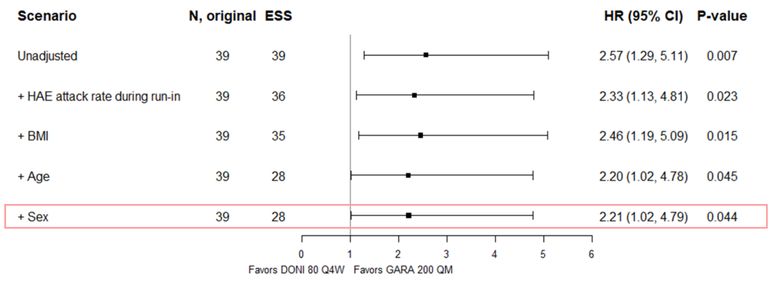


Figure 2 (A,B,C): Base Case Analysis for GARA 200 QM vs. DONI 80 Q8W

Figure 2A: Time-normalized number of HAE attacks GARA 200 QM vs. DONI 80 Q8W

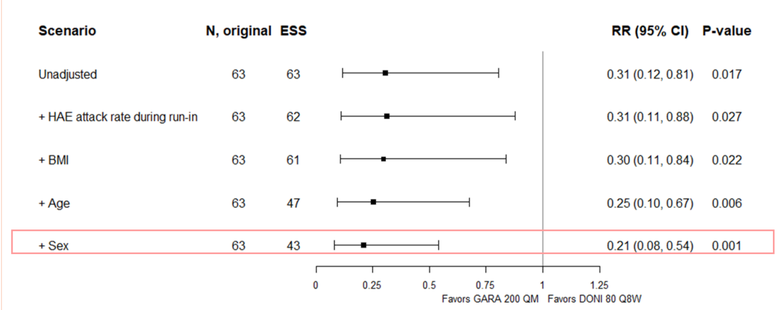


Figure 2B: Time-normalized number of moderate and/or severe HAE attacks GARA 200 QM vs. DONI 80 Q8W

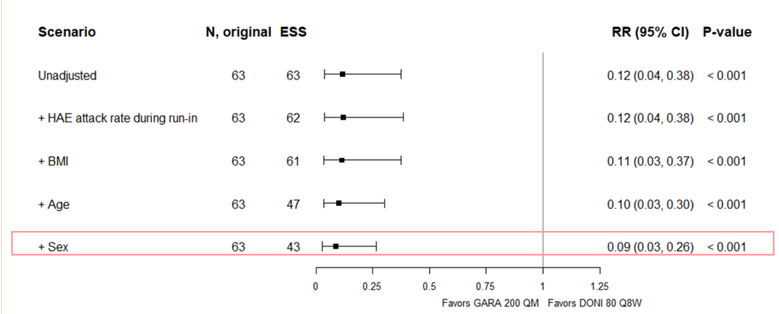
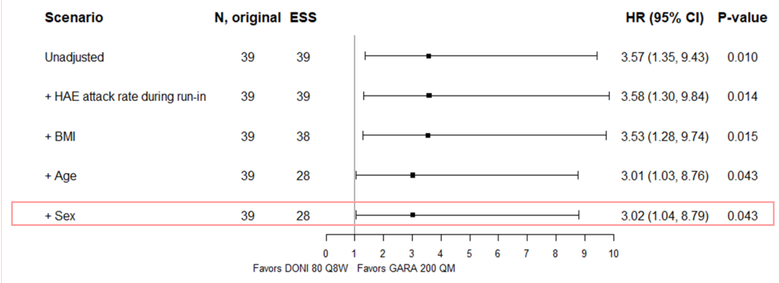


Figure 2C: Proportion of attack-free patients over the trial period GARA 200 QM vs. DONI 80 Q8W



Note:
- These forest plots show results of the unadjusted analysis, and subsequent analyses which adjust for each new variable incrementally. The base case analysis adjusted for all available factors is indicated by a pink box.
- ESS is rounded to whole numbers.

Limitations

- Differences in trial design, eligibility criteria, and outcome definitions between the VANGUARD and OASIS-HAE trials may affect comparability. Although clinically relevant covariates were adjusted for using MAIC, residual confounding due to unmeasured or unreported variables cannot be ruled out.
- The unanchored MAIC used for the attack-free outcome relies on stronger assumptions than anchored analyses, including the need to account for all effect modifiers and prognostic factors, which may not be fully captured in published data. However, the prognostic differences between trials may be minimal given that one patient in OASIS-HAE and ISIS 721744-CS2, and zero patients in VANGUARD, achieved attack-free status in the placebo arms of these trials.

CONCLUSIONS

- **These consistent findings suggest that garadacimab may provide improved therapeutic benefit compared to donidalorsen for LTP in HAE.**
- **GARA 200 QM demonstrated statistically significant improvements over DONI 80 Q4W and Q8W across all evaluated outcomes, with the exception of time-normalized number of HAE attacks, in which GARA 200 QM demonstrated a numerical benefit over DONI 80 Q4W.**

ABBREVIATIONS:
BMI = Body mass index
CI = confidence interval
DONI 80 Q4W = Donidalorsen 80 mg administered subcutaneously every four weeks
DONI 80 Q8W = Donidalorsen 80 mg administered subcutaneously every eight weeks
EMA = European Medicines Agency
ESS = Effective sample size
FDA = United States Food and Drug Administration
GARA 200 QM = Garadacimab 200 mg administered subcutaneously once monthly
HAE = Hereditary angioedema
HR = Hazard ratio
IPD = Individual patient data
LTP = Long-term prophylaxis
MAIC = Matching-adjusted indirect comparison
RR = Rate ratio

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*** FOOTNOTES FOR TABLES:**
Bold values indicate statistical significance and correspond to a two-tailed p-value <0.05.
An RR <1 indicates an improved outcome for GARA 200 QM relative to DONI 80 Q4W or DONI 80 Q8W.
An HR >1 indicates an improved outcome for GARA 200 QM relative to DONI 80 Q4W or DONI 80 Q8W.
[a] Analyses adjusted for the following variables: HAE attack rate during run-in, BMI, age, and sex.
[b] The analysis includes data from the Phase 3 (VANGUARD) garadacimab trial and the Phase 3 (OASIS-HAE) donidalorsen trial.
[c] The sensitivity analysis includes pooled data from the Phase 2 (ISIS 721744-CS2) and Phase 3 (OASIS-HAE) donidalorsen trials and pooled data from the Phase 2 (CSL312_2001) and Phase 3 (VANGUARD) garadacimab trials.
[d] For the base case analysis and the pooled Phase 2 & 3 and race sensitivity analyses, estimates for GARA 200 QM vs placebo were derived from a quasi-Poisson model with log link function. Treatment group was included as a covariate and the logarithm of patient-level follow-up time in months was included as an offset. For the sensitivity analysis emulating the comparator model, estimates for GARA 200 QM vs placebo were derived from a Poisson model with log link function. Pearson chi-square scaling of standard errors was used to account for potential overdispersion. Treatment group, baseline (i.e., HAE attack-rate during run-in), and the treatment-by-baseline interaction were included as covariates and the logarithm of patient-level follow-up time in months was included as an offset.
[e] Across all analyses, estimates for GARA 200 QM vs placebo were derived from a quasi-Poisson model with log link function. Treatment group was included as a covariate and the logarithm of patient-level follow-up time in months was included as an offset.
[f] Unanchored MAICs were conducted for the proportion of attack-free patients outcome since anchored MAICs were not feasible. Estimates for GARA 200 QM vs DONI were derived from a Binomial model with complementary log-log link function. Treatment group was included as a covariate and the logarithm of patient-level follow-up time in days was included as an offset.
[g] Analysis only includes data from the Phase 3 (OASIS-HAE) donidalorsen trial since DONI 80 Q8W was not reported in the Phase 2 (ISIS 721744-CS2) donidalorsen trial.

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