SUPPLEMENTARY MATERIAL

Efgartigimod and ravulizumab for treating acetylcholine receptor autoantibodies positive (AChR-Ab+) generalized myasthenia gravis: indirect treatment comparison

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Supplementary Material 1: ITC Methods

Population adjustments

Following NICE recommendations [1], only the treatment effect modifiers, both balanced and unbalanced between the studies, were used to adjust the population characteristics. The selected treatment effect modifiers were based on the stratification variables used in the ADAPT sub-group analyses. As a result, the following baseline characteristics were used in the matching-adjusted indirect comparison (MAIC):

- Time from diagnosis to randomization
- Use of glucocorticoids at baseline
- Use of other non-steroidal immunosuppressive drugs at baseline
- MG-ADL score at baseline.

The efgartigimod effect was adjusted by applying a specific weight to each patient. The weights were calculated by minimizing the following function:

$$\sum_i \exp\left(\boldsymbol{\alpha^T} X_i^{EM}\right)$$

where:

X_i^{EM} was a matrix that contained the values of the selected covariates (effect modifiers) in ADAPT, centred around the mean of the corresponding covariate in CHAMPION.

$\boldsymbol{\alpha^T}$ was a vector containing the parameters to be optimized.

The weight of each patient *I* (w_i) was then calculated by taking:

$$w_i = \exp\left(X_i^{EM} \boldsymbol{\alpha^T}\right)$$

Outcomes: Area under the curve (AUC)

Estimating AUC for efgartigimod and placebo from ADAPT

The AUC of the change from baseline up to week 26 in the MG-ADL, QMG, and MG-QoL15 scores was calculated using IPD from the ADAPT study. An ANCOVA model was fitted to the data with AUC as the outcome variable, and treatment arm, baseline score of MG-ADL/QMG/MG-QoL15, and two stratification factors (Japanese vs non-Japanese ethnicity; use of corticosteroid at baseline) as covariates. The relative treatment effect of efgartigimod vs placebo was given by the difference in the least squares means obtained from the ANCOVA model.

To estimate the AUC, the ADAPT records were analyzed as a continuous sequence, rather than cycle by cycle. All assessments were re-allocated to the analysis windows defined in Table 1. For each analysis window, the value closest to the target distance from baseline was used in the analysis. If multiple values were located at the same distance from the target, the latest in time was selected. Using the IPD, the AUC was derived by applying the trapezoidal rule on all non-missing values from available analysis visits up to week 26. Applying the trapezoidal rule, the total AUC was divided into smaller trapezoids and the area of each single trapezoid was calculated. The trapezoids were defined according to the observed timepoints (*t*) and their area was calculated using the following formula:

$$x_n \approx (t_{+1} - t)\frac{1}{2}(y_t + y_{t+1})$$

Where:

x_n represents the area of the trapezoid between timepoint *t* and timepoint $t + 1$

y_t and y_{t+1} represent, respectively, the MG-ADL change from baseline at timepoint t and timepoint $t + 1$.

The AUC was estimated as the sum of the trapezoid areas (x_n). In case of a time gap between the last available value and week 26, the missing time period was extrapolated by the average status observed for the specific patient. For example, this means that if the last analysis visit with evaluable values was week 24, the AUC was calculated up to week 24 (AUC_{24}). Then, the time averaged status $AUC_{24}/24$ was carried forward through week 26, i.e., $ACU_{26} = AUC_{24} + 2 * (AUC_{24}/24)$.

Table 1. Analysis visit windows.

Analysis window	Target distance from baseline, days	Lower limit, days	Upper limit, days
Baseline	1	-Infinity	1
Week 1	8	2	11
Week 2	15	12	18
Week 3	22	19	25
Week 4	29	26	32
Week 5	36	33	39

Week 6	43	49	46
Week 7	50	47	53
Week 8	57	54	63
Week 10	71	64	77
Week y	y*7 + 1	y*7 - 6	y*7 + 7

Estimating AUC for ravulizumab and placebo from CHAMPION

Since IPD from CHAMPION study were not available, it was not possible to estimate the AUC of the change from baseline up to 26 weeks at the individual patient level. Thus, the AUC of ravulizumab and the placebo arm were estimated at the aggregate level by digitizing the graphs of the change from baseline in the CHAMPION publication [2]. As described in that publication, the change from baseline for ravulizumab and placebo was estimated as the least squares means obtained from a mixed model for repeated measurements, with the observed MG-ADL, QMG or MGQoL-15 value as the outcome variable and treatment arm and baseline MG-ADL/QMG/MGQoL-15 score as covariates. Thus, this model controls for potential confounding factors. The points of change from baseline over time were reconstructed via digitization of the graphs in the study publication [2] using Engauge Digitizer (Table 2).

Table 2. Reconstructed MG-ADL, QMG, and MGQoL-15 change from baseline in CHAMPION.

Week	Change from baseline, mean (95% CI)					
	MG-ADL		QMG		MG-QoL15	
	Ravulizumab	Placebo	Ravulizumab	Placebo	Ravulizumab	Placebo
1	-1.7 (-2.3, -1.1)	-0.9 (-1.5, -0.3)	-1.6 (-2.3, -1.0)	-0.5 (-1.2, 0.2)	N/A	N/A
2	-1.8 (-2.4, -1.2)	-1.3 (-1.9, -0.7)	-2.3 (-3.1, -1.6)	-0.6 (-1.4, 0.1)	N/A	N/A
4	-2.6 (-3.2, -1.9)	-1.5 (-2.1, -0.8)	-2.6 (-3.4, -1.7)	-0.8 (-1.6, 0.0)	-3.2 (-4.5, -2.0)	-1.6 (-2.8, -0.3)
10	-2.8 (-3.5, -2.1)	-1.3 (-2, -0.6)	-2.7 (-3.6, -1.9)	-0.9 (-1.7, 0.0)	N/A	N/A
12	-3.3 (-3.9, -2.6)	-2.2 (-2.9, -1.5)	-2.8 (-3.7, -1.9)	-1.5 (-2.4, -0.7)	-3.8 (-5.1, -2.5)	-2.1 (-3.4, -0.8)
18	-3.1 (-3.9, -2.4)	-1.9 (-2.6, -1.1)	-3.2 (-4.1, -2.3)	-1.1 (-2.1, -0.2)	-3.3 (-4.7, -1.9)	-2.3 (-3.6, -1)
26	-3.1 (-3.8, -2.3)	-1.4 (-2.1, -0.7)	-2.8 (-3.7, -1.9)	-0.8 (-1.7, 0.1)	-3.7 (-5.1, -2.4)	-1.6 (-3, -0.3)

Abbreviations: CI, Confidence Interval.

Outcomes: Change from baseline

The CHAMPION and the ADAPT studies measured the MG-ADL, QMG, and MG-QoL15 scores at different timepoints. The ADAPT study reported the scores at multiple timepoints up to week 26. The CHAMPION study reported the change from baseline on the scores only at week 26. However, charts were presented which showed the change in the scores at different timepoints up to week 26 [2].

In ADAPT, the efgartigimod maximum effect on the overall cohort was observed at week 4. Despite not being explicitly stated in the CHAMPION study, the peak effect of ravulizumab is expected at 26 weeks (primary endpoint measured at 26 weeks). However, the changes from baseline in MG-ADL, QMG, and MG-QoL15 in the ravulizumab arm do not follow a constant rate to week 26, rather a large part of the total change in disease activity was observed at week 4, with a smaller change from week 4 to week 26. For this reason, two analyses were conducted comparing the change from baseline in MG-ADL, QMG, and MG-QoL15 at:

- Time of best response: week 4 for efgartigimod and week 26 for ravulizumab
- Week 4 for both efgartigimod and ravulizumab (for this comparison, the outcome in ravulizumab arm was reconstructed by digitising the graph presented in the CHAMPION publication [2]).

Outcomes: Minimum point improvements in MG-ADL total score from baseline

In CHAMPION, the proportion of patients achieving a MG-ADL reduction of at least 3, 4, or 5 points from baseline at week 26 was reported [2]. No data on this outcome were reported at week 4 and therefore the MAIC on the proportion of patients achieving a given MG-ADL point reduction was conducted only at time of best response (week 4 for efgartigimod and week 26 for ravulizumab). This outcome was not reported in ADAPT, and so it was defined using the IPD. For CHAMPION, the standard error for each percentage point was calculated assuming normality as IPD were not available.

Outcomes: Number needed to treat (NNT)

The NNT was estimated as the reciprocal of the proportion of patients achieving a given MG-ADL reduction. Thus, as described in the section above, the comparison of NNT could only be conducted at the time of best response.

Adjusted treatment effects

For the AUC outcomes, the adjusted relative treatment effects of efgartigimod vs placebo were estimated as the difference in least squares (LS) mean from ANCOVA models fitted to the ADAPT IPD, with AUC as the independent variable and the treatment arm, baseline value, and two stratification factors (Japanese/non-Japanese ethnicity; receiving of non-steroidal immunosuppressive drug at baseline) as covariates. The ANCOVA models used the weights calculated with the MAIC as frequency weights. The relative treatment effect of efgartigimod vs ravulizumab was estimated as the adjusted treatment effect

of efgartigimod vs placebo estimated from the ANOVA model minus the relative treatment effect of ravulizumab vs placebo (observed from the CHAMPION MG study). The standard error (SE) of any difference was calculated considering both random variation between subjects and fixed effects variation within subject. Since IPD data from CHAMPION were not available for these analyses, it was not possible to define how much of the random variation accounts for total variation. Therefore, it was assumed that the CHAMPION study had similar random vs fixed effects to those observed in the IPD of the ADAPT study.

For the change from baseline outcomes, the adjusted relative effects of efgartigimod vs placebo were calculated using the LS mean obtained by mixed models for repeated measures that used the estimated weights as frequency weights. All available data up to week eight were included. The model included treatment, visit, and treatment by visit interaction terms as fixed effects, with baseline value, and stratification factors (Japanese vs non-Japanese ethnicity; use of corticosteroid at baseline) as covariates. Within-subject correlation was modelled by assuming an unstructured covariance matrix for the error terms. The MMRM was chosen to align with ADAPT and CHAMPION, which used the same model for the inferential statistics. The relative effect of efgartigimod vs ravulizumab was estimated as the adjusted relative effect of efgartigimod vs placebo (based on the above MMRM model) minus the relative effect of ravulizumab vs placebo observed in the CHAMPION MG study.

The proportion of the cohort experiencing an improvement of ≥3, ≥4, or ≥5 for MG-ADL at week 4 in ADAPT was calculated using a weighted generalized linear model with identity link and treatment arm and baseline value as covariates. The model was weighted to adjust for the MAIC analysis. The difference between efgartigimod and ravulizumab was estimated by taking the difference between the adjusted relative effect of efgartigimod vs placebo and the observed relative effect of ravulizumab vs placebo.

References

1. Phillippo, D.M., et al., *Methods for Population-Adjusted Indirect Comparisons in Health Technology Appraisal.* Med Decis Making, 2018. **38**(2): p. 200-211.
2. Vu, T., et al., *Terminal Complement Inhibitor Ravulizumab in Generalized Myasthenia Gravis.* NEJM Evidence, 2022. **1**(5).