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BRIEF REPORT

Efgartigimod and Ravulizumab for Treating Acetylcholine Receptor Auto-antibody-Positive (AChR-Ab+) Generalized Myasthenia Gravis: Indirect Treatment Comparison

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ABSTRACT

Introduction: Efgartigimod and ravulizumab, both approved for treating acetylcholine receptor auto-antibody-positive (AChR-Ab+) generalized myasthenia gravis (gMG), have not been directly compared. This paper assessed comparative effects of efgartigimod vs. ravulizumab for treating adults with AChR-Ab+ gMG using indirect treatment comparison methods.

Methods: The matching-adjusted indirect comparison used data from two randomized trials of adult men and women. The ADAPT (efgartigimod vs. placebo; individual patient data available) population was reweighted to match the CHAMPION (ravulizumab vs. placebo; index study; aggregate data available) population. The relative effect of efgartigimod versus placebo was estimated in this reweighted population and compared with the observed ravulizumab versus placebo effect to estimate the efgartigimod versus ravulizumab effect. The outcomes were Myasthenia Gravis Activities of Daily Living (MG-ADL), Quantitative Myasthenia Gravis (QMG), and Myasthenia Gravis Quality of Life 15-item-revised scale (MG-QoL15r) assessed as cumulative effect (area under the curve; AUC) over 26 weeks (primary) and change from baseline at 4 weeks and time of best response (week 4 for efgartigimod; week 26 for ravulizumab).

Results: For MG-QoL15r, efgartigimod had a statistically significant improvement compared with ravulizumab over 26 weeks [mean difference (95% confidence interval): – 52.6 (– 103.0, – 2.3)], at week 4 [– 4.0 (– 6.6, – 1.4)], and at time of best response [– 3.9 (– 6.5, – 1.3)]. Efgartigimod had a statistically significant improvement over ravulizumab in MG-ADL at week 4 [– 1.9 (– 3.3, – 0.5)] and at time of best response [– 1.4 (– 2.8, 0.0)] and in QMG at week 4 [– 3.2 (– 5.2, – 1.2)] and at time of best response [– 3.0 (– 5.0, – 1.0)]. For AUC over 26

Prior Presentation: Part of this study has been presented at the ISPOR EU conference 2022 (https://www.ispor.org/docs/default-source/euro2022/isporposterco15-pdf.pdf?sfvrsn=caa19006_0).

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weeks, improvements were not significantly different between efgartigimod and ravulizumab for MG-ADL [– 8.7 (– 36.1, 18.8)] and QMG [– 13.7 (– 50.3, 22.9)].
Conclusion: Efgartigimod may provide a faster and greater improvement over 26 weeks in quality of life than ravulizumab in adults with AChR-Ab+ gMG. Efgartigimod showed faster improvements in MG-ADL and QMG than ravulizumab.

Keywords: Acetylcholine receptor auto-antibodies positive; AChR-Ab+ ; Efgartigimod; Generalized myasthenia gravis; MG-ADL; MG-QoL15; QMG; Ravulizumab

Key Summary Points

Why carry out this study?

Although efgartigimod and ravulizumab are both approved for treating acetylcholine receptor auto-antibody-positive (AChR-Ab+) generalized myasthenia gravis (gMG), they have not been compared in a head-to-head study.

To address this gap, this study conducted an indirect treatment comparison assessing the relative efficacy of efgartigimod versus ravulizumab in adults with AChR-Ab+ gMG.

What was learned from the study?

Efgartigimod was associated with a statistically significant improvement compared with ravulizumab in terms of Myasthenia Gravis Quality of Life 15-item-revised scale (MG-QoL15r).

Findings were mixed for Myasthenia Gravis Activities of Daily Living (MG-ADL) and Quantitative Myasthenia Gravis (QMG), with efgartigimod showing a significant improvement over ravulizumab at week 4 and at time of best response, but not over 26 weeks.

The results suggest that efgartigimod provides a faster and greater improvement over 26 weeks in quality of life than ravulizumab in adults with AChR-Ab+ gMG.

INTRODUCTION

Generalized myasthenia gravis (gMG) is a rare, chronic, neuromuscular autoimmune disease, mediated by pathogenic immunoglobulin auto-antibodies targeting the neuromuscular junction [1]. gMG is a debilitating disease that negatively impacts patients' activities of daily living and has severe negative impact on patients' quality of life [2, 3]. Conventional therapy for gMG include acetylcholinesterase inhibitors, mainly pyridostigmine, with or without corticosteroids, as well as nonsteroidal immunosuppressive therapies, such as azathioprine, mycophenolate mofetil, methotrexate, ciclosporin, or tacrolimus [4]. Immunoglobulin and plasma exchange may be used as maintenance treatment in patients with active disease despite use of conventional therapy [4].

Efgartigimod and ravulizumab have been approved for the treatment of acetylcholine receptor auto-antibody-positive (AChR-Ab+) gMG. Both drugs were studied in gMG patients in separate placebo-controlled randomized controlled trials (RCTs). An understanding of the comparative benefits of these two therapies would support the decision-making process in gMG treatment; however, no direct comparative evidence exists.

The effect of efgartigimod in gMG was investigated in the ADAPT study, a double-blind, placebo-controlled, phase 3 multicenter RCT [1], followed by an open label extension (ADAPT+; NCT03770403). Adult patients with a diagnosis of gMG (regardless of serotype) were eligible to participate if they had a score of at least five on the Myasthenia Gravis Activities of Daily Living (MG-ADL) scale, which is a validated clinical endpoint to measure the disease

activity in gMG that is often used in clinical trials [5].

The effect of ravulizumab in gMG was investigated in the CHAMPION MG study, a double-blind, placebo-controlled, phase 3 RCT [6], followed by an open label extension [7]. Adult patients with AChR-Ab+ gMG were eligible to participate in the trial if they had a MG-ADL score of six or higher.

Efgartigimod and ravulizumab had different treatment schedules in these trials. In ADAPT, four infusions of efgartigimod were administered during a period of 3 weeks (one infusion per week) [1]. All patients received an initial cycle; subsequent cycles were initiated according to each patient's clinical evaluation (MG-ADL total score $\geq$ 5 points with more than 50% of the total score due to non-ocular symptoms and loss of clinically meaningful improvement in MG-ADL score) for individualized treatment intervals due to the fluctuating nature of the disease. Subsequent cycles started at least 8 weeks from initiation of the previous cycle. A maximum of three cycles was possible in the 26-week trial and the timing of initiation of a new cycle may have differed between patients depending on their clinical status. Conversely, in CHAMPION, all patients had the same treatment schedule for ravulizumab [6]. They received an initial loading dose of ravulizumab at baseline, followed by maintenance doses on day 15 and every 8 weeks thereafter.

Both RCTs included both men and women. Sex differences are not expected for these treatments, therefore sex was not adjusted for within the analyses.

The aim of this paper was to assess comparative effects of efgartigimod versus ravulizumab for the treatment of adult patients with AChR-Ab+ gMG using indirect treatment comparison (ITC) methods to aid clinical decision-making. The research hypothesis was that efgartigimod and ravulizumab, due to having different mechanisms of action, may result in a different speed of onset [1].

METHODS

Overall Approach

These analyses used data from two existing RCTs (ADAPT [1] and CHAMPION [6])] and therefore no additional data collection was undertaken.

There were three main steps to conducting the ITC. First, the ADAPT population were aligned to the CHAMPION population by excluding ADAPT patients from the analyses if they would have been ineligible for the CHAMPION study, and then assigning weights to the remaining ADAPT patients based on baseline characteristics so that the reweighted ADAPT population had similar baseline characteristics to the CHAMPION population [9]. Second, the relative effect of efgartigimod versus placebo was estimated in this reweighted ADAPT population, allowing estimation of the relative effect of efgartigimod versus placebo as if efgartigimod was administered to the CHAMPION population. Third, the estimated relative effect of efgartigimod versus placebo in the reweighted population was compared with the observed ravulizumab versus placebo effect in the CHAMPION RCT to estimate the efgartigimod versus ravulizumab effect.

The ITC method used to conduct these steps was matching-adjusted indirect comparison (MAIC), because individual patient data (IPD) were available for ADAPT, whereas only the published aggregate-level data were available for the CHAMPION study [6, 8]. Because a placebo arm was included in both ADAPT and CHAMPION, a MAIC anchored to the placebo arm was conducted [8]. The MAIC approach assumes that the treatment relative effect is constant, conditional on the two populations having the same level of the effect modifiers.

Alignment of ADAPT Population to CHAMPION Population

The first step was to restrict the ADAPT population to align with the inclusion/exclusion criteria used in CHAMPION as far as possible:

- Only patients with AChR-Ab+ gMG were recruited in CHAMPION, therefore only ADAPT patients with AChR-Ab+ gMG were included in the analysis.
- In CHAMPION, patients diagnosed with gMG in the six months before randomization were excluded, while in ADAPT there were no restrictions on the time from diagnosis. Therefore, the ADAPT patients with a gMG diagnosis within 6 months of baseline were excluded.
- In CHAMPION, only patients with a baseline MG-ADL score ≥ 6 points were included. In ADAPT, the analogous threshold was 5 points. Therefore, ADAPT patients with a baseline MG-ADL score of 5 were excluded.
- The ADAPT study excluded patients with a thymectomy in the prior 3 months, while CHAMPION excluded patients with a thymectomy in the prior 6 months. Therefore, the ADAPT patients treated with a thymectomy between 3 and 6 months before baseline were excluded.

Following this, treatment effect modifiers based on the stratification variables used in the ADAPT sub-group analyses were used to adjust the population characteristics (see the electronic supplementary material for details).

Outcomes

The measures of interest were MG-ADL, Quantitative Myasthenia Gravis (QMG), and Myasthenia Gravis Quality of Life 15-item-revised scale (MG-QoL15r). These scales are validated and often used to measure the severity of gMG, with a higher score indicating worse severity [5, 10, 11]. MG-ADL is an 8-item question questionnaire (total score from 0 to 24) that assesses the impact of myasthenia gravis and its symptoms on daily living, and is a common primary endpoint in RCTs [5]. QMG is a 13-item direct physician assessment (total score from 0 to 39) based on impairments of body functions and structures [10]. MG-QoL15r is a 15-item questionnaire (total score 0–60) that estimates QoL relevant to myasthenia gravis [11].

MAIC analyses were performed on the following outcomes:

- The AUC of the reduction in disease symptoms (based on MG-ADL, QMG, and MG-QoL15r) over 26 weeks (primary analyses).
- The change from baseline versus placebo at week 4 and at time of best response over the 26-week study period selected as the time of the lowest average MG-ADL score for each treatment (4 weeks for efgartigimod and 26 weeks for ravulizumab) in MG-ADL, QMG, and MG-QoL15r.
- The proportion of cohort with ≥ 3, ≥ 4, or ≥ 5 points reduction in MG-ADL at the time of best response.
- The number needed to treat (NNT), defined as the number of patients that need to be treated to observe ≥ 3, ≥ 4, or ≥ 5 points reduction in MG-ADL at the time of best response.

The electronic supplementary material provides details on how each of these measures were derived.

Statistical Analysis

The electronic supplementary material provides details on how the adjusted relative treatment effects for efgartigimod versus ravulizumab were estimated. Analyses were conducted in R v4.0 ® Foundation for Statistical Computing, Vienna, Austria) and SAS v9.4 (SAS Institute, Cary NC, USA).

Effective Sample Size (ESS)

The sample size for the analysis was driven by the sample sizes of the source data as no extra data were collected for these analyses.

"The ESS represents the number of independent non-weighted individuals that would be required to give an estimate with the same precision as the weighted sample estimate" [8]. In other words, the results obtained with the reweighted sample have the same statistical precision as the results that would be obtained with a normal, non-weighted sample whose size equals the ESS. Hence, if the ESS is very small, it indicates that the weighting has dramatically reduced the precision of the results. Conversely,

Table 1 Baseline characteristics in people with AChR-Ab+ gMG who were included in the ADAPT and CHAMPION studies

Characteristic	ADAPT[a]			CHAMPION		
	Total ($n = 111$)	Efgartigimod ($n = 55$)	Placebo ($n = 56$)	Total ($n = 175$)	Ravulizumab ($n = 86$)	Placebo ($n = 89$)
	Mean (SD)					
Age at enrolment, years	47.3 (15.8)	45.0 (15.5)	49.7 (15.7)	55.6 (15.1)	58 (13.8)	53.3 (16.1)
Age at diagnosis, years	37.6 (18.0)	35.2 (17.8)	39.9 (18.1)	46.1 (18.9)	48.6 (18.5)	43.7 (19)
Years from diagnosis to randomization	9.8 (8.4)	9.8 (8.6)	9.8 (8.3)	9.9 (9.3)	9.8 (9.7)	10 (8.9)
Baseline clinical disease activity						
MG-ADL score	9.2 (2.1)	9.5 (2.2)	8.8 (2.0)	9.0 (2.5)	9.1 (2.6)	8.9 (2.3)
QMG score	15.8 (4.8)	16.3 (5.2)	15.3 (4.3)	14.7 (5.2)	14.8 (5.2)	14.5 (5.3)
MG-QoL15r score	16.8 (5.5)	16.4 (5.8)	17.2 (5.2)	–	–	–
	Count (%)					
Woman	75 (67.6)	40 (72.7)	35 (62.5)	89 (50.9)	44 (51.2)	45 (50.6)
Race/ethnicity						
Asian	10 (9.0)	6 (10.9)	4 (7.1)	31 (17.7)	15 (17.4)	16 (18.0)
African/American	2 (1.8)	0 (0.00)	2 (3.6)	6 (3.4)	2 (2.3)	4 (4.5)
White	95 (85.6)	46 (83.6)	49 (87.5)	128 (73.1)	67 (77.9)	61 (68.5)
Other	3 (2.7)	3 (5.4)	0 (0.00)	3 (1.7)	0 (0.0)	3 (3.4)
Not reported	1 (0.9)	0 (0.00)	1 (1.8)	7 (4.0)	2 (2.3)	5 (5.6)
Current/previous treatments						
Prior thymectomy	62 (55.9)	36 (65.5)	26 (46.4)	–	–	–
Glucocorticoids	84 (75.7)	39 (70.9)	45 (80.4)	121 (69)	56 (65)	65 (73)
Other NSID	66 (59.5)	33 (60.0)	33 (58.9)	119 (68)	56 (65)	63 (71)
MGFA clinical class						
Class I	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Class II	43 (38.7)	20 (36.3)	23 (41.1)	78 (44.6)	39 (45.3)	39 (43.8)
Class III	63 (56.8)	33 (60.0)	30 (53.6)	86 (49.1)	41 (47.7)	45 (50.6)
Class IV	5 (4.5)	2 (3.6)	3 (5.4)	11 (6.3)	6 (7.0)	5 (5.6)

AChR-Ab+ acetylcholine receptor auto-antibody-positive, *gMG* generalized Myasthenia Gravis, *MGFA* Myasthenia Gravis Foundation of America, *NSID* non-steroidal immunosuppressive drug, *SD* standard deviation, – indicates that data were not reported

[a]Demographics are shown for the 111 patients in the ADAPT study who were included in the analyses presented in this manuscript

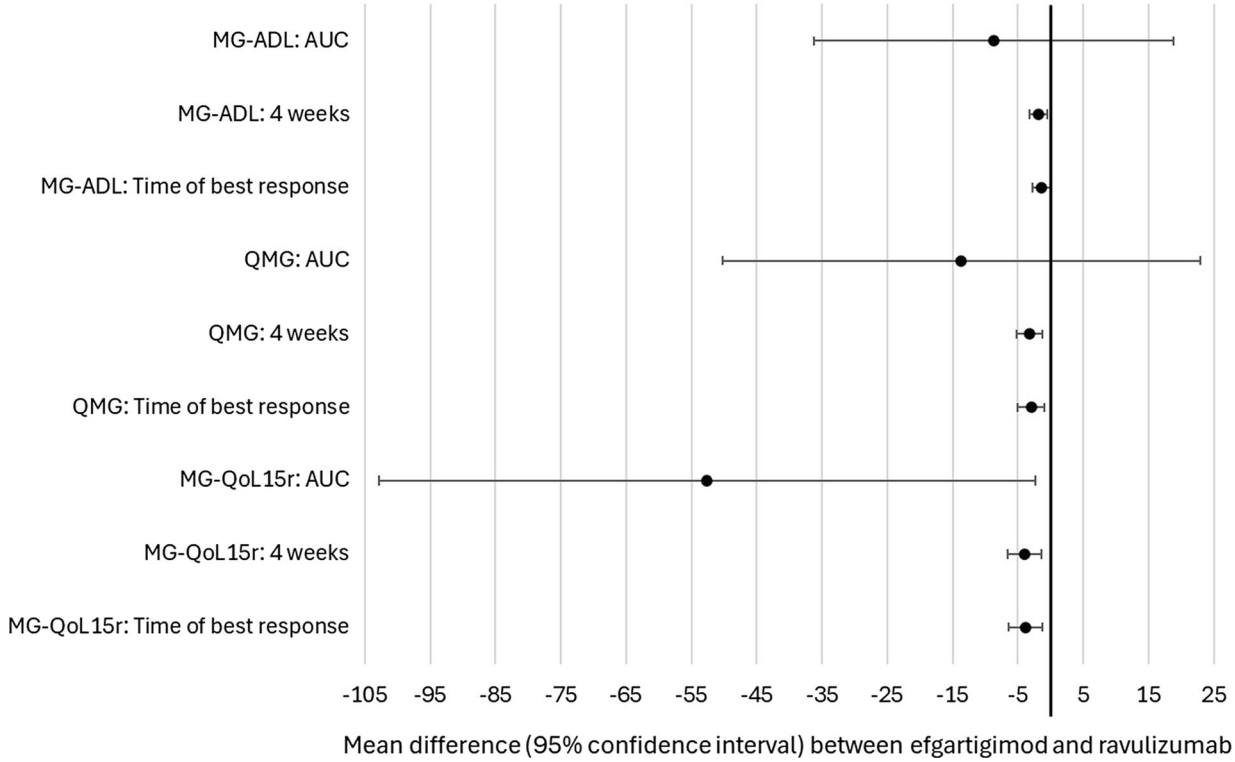

Fig. 1 Forest plot summarizing matching-adjusted indirect comparison results comparing efgartigimod and ravulizumab for the treatment of acetylcholine receptor auto-antibodies-positive (AChR-Ab+) generalized myasthenia gravis (gMG) in adults. *AUC* area-under-the-curve, *MG-ADL* Myasthenia Gravis Activities of Daily Living, *MG-QoL15r* Myasthenia Gravis Quality of Life 15-item-revised scale, *QMG* Quantitative Myasthenia Gravis. Values below 0 favor efgartigimod; values above 0 favor ravulizumab; results at 4 weeks represent a change from baseline to 4 weeks; results at time of best response represent a change from baseline to week 4 for efgartigimod and to week 26 for ravulizumab

a larger ESS implies more stable results. Therefore, the ESS was calculated for each MAIC that was conducted using standard methodology [8].

Ethical Approval

This article is based on previously conducted studies and does not contain any new studies with human participants or animals performed by any of the authors, therefore IRB approval was not required. In this indirect treatment comparison, no real-life patients were included and IRB approval was therefore not required.

RESULTS

Study Populations and Matching

Table 1 shows the baseline characteristics of participants in the ADAPT and CHAMPION studies. After restricting the ADAPT cohort to align with the inclusion/exclusion criteria used in CHAMPION, the AUC analyses were based on 111 patients for MG-ADL and MG-QoL15r and on 109 patients for QMG. The change from baseline analyses were based on 108 patients for MG-ADL and MG-QoL15r and on 105 patients for QMG. The minimum point improvements in MG-ADL from baseline and NNTs were also based on 108 patients. Data from all 175 CHAMPION participants were analyzed.

Table 2 Relative effect of efgartigimod versus ravulizumab in terms of AUC for MG-ADL, QMG and MG-QoL15r change from baseline over 26 weeks follow-up in people with AChR-Ab+ gMG derived using MAIC

	AUC					
	MG-ADL		QMG		MG-QoL15r	
	n	Mean (95% CI)	*n*	Mean (95% CI)	*n*	Mean (95% CI)
Adjusted results estimated using reweighted data from the ADAPT study						
Efgartigimod	55	− 62.2 (− 86.8, − 37.7)***	55	− 73.8 (− 107.4, − 40.3)***	55	− 121.9 (− 166.6, − 77.2)***
Placebo	56	− 22.0 (− 46.8, 2.9)	54	− 14.0 (− 48.4, 20.3)	56	− 31.3 (− 76.4, 13.8)
Efgartigimod vs. placebo	111	− 40.3 (− 62.5, − 18.0)**	109	− 59.8 (− 91.0, − 28.5)**	111	− 90.6 (− 130.5, − 50.8)***
Results estimated from the CHAMPION study						
Ravulizumab	86	− 73.3 (− 90.8, − 55.3)***	86	− 70.9 (− 93.0, − 49.0)***	86	− 84.6 (− 116.8, − 53.6)***
Placebo	89	− 41.8 (− 59, − 23.5)***	89	− 24.8 (− 47.6, − 3.4)*	89	− 46.6 (− 77.6, − 15.2)**
Ravulizumab vs. placebo	175	− 31.6 (− 56.7, − 6.4)***	175	− 46.1 (− 77.2, − 14.9)***	175	− 38.0 (− 69.4, − 6.6)*
MAIC results anchored on above comparisons with placebo						
Efgartigimod vs. ravulizumab	141	− 8.7 (− 36.1, 18.8)	141	− 13.7 (− 50.3, 22.9)	141	− 52.6 (− 103.0, − 2.3)*

AChR-Ab+ acetylcholine receptor auto-antibody-positive, *AUC* Area Under the Curve, *CI* Confidence Interval, *gMG* generalized Myasthenia Gravis, *MAIC* Matching-Adjusted Indirect Comparison, *MG-ADL* Myasthenia Gravis Activities of Daily Living, *MG-QoL15r* Myasthenia Gravis Quality of Life 15-item-revised scale, *QMG* Quantitative Myasthenia Gravis
*p value < 0.05; **p value < 0.01; ***p value < 0.001

The MAIC ESS for the ADAPT population was 102.39 for the analyses on MG-ADL, 94.06 for those on QMG, and 102.42 for those on MG-QoL15r. These represented approximately 92% and 86% of the sample sizes in the MG-ADL/MG-QoL15r and QMG MAIC analyses, respectively.

Overall Findings

The main findings of the MAICs comparing efgartigimod and ravulizumab for each endpoint are summarized in Fig. 1, with more details in the remainder of this Results section.

AUC for MG-ADL, QMG and MG-QoL15r

Compared with placebo, efgartigimod was associated with statistically significant greater cumulative improvement in MG-ADL, QMG, and MG-QoL15r over the 26-week follow-up period, following reweighting of the IPD in ADAPT (Table 2).

Compared with placebo, ravulizumab was also associated with statistically significant greater cumulative improvement in MG-ADL and QMG, but not in MG-QoL15r.

In the MAIC on the AUC, efgartigimod was associated with a statistically significant improvement in MG-QoL15r compared with ravulizumab over 26 weeks (− 52.6 [− 103.0,

Table 3 Relative effect of efgartigimod versus ravulizumab in terms of change from baseline at week 4 and at time of best response for MG-ADL, QMG and MG-QoL15r in people with AChR-Ab+ gMG derived using MAIC

	Change from baseline					
	MG-ADL		QMG		MG-QoL15r	
	N	Mean (95% CI)	*N*	Mean (95% CI)	*N*	Mean (95% CI)
Adjusted results estimated using reweighted data from the ADAPT study						
Week 4 (time of best response)						
Efgartigimod	53	− 4.3 (− 5.3, − 3.3)***	52	− 5.6 (− 7.1, − 4.2)***	53	− 7.6 (− 9.4, − 5.8)***
Placebo	55	− 1.3 (− 2.3, − 0.3)**	53	− 0.7 (− 2.1, 0.7)	55	− 2.0 (− 3.8, − 0.2)
Efgartigimod vs. placebo	108	− 3.0 (− 4.0, − 2.0)***	105	− 5.0 (− 6.6, − 3.4)***	108	− 5.6 (− 7.6, − 3.6)***
Results estimated from the CHAMPION study						
Week 4						
Ravulizumab	84	− 2.6 (− 3.2, − 1.9)***	79	− 2.6 (− 3.4, − 1.7)***	85	− 3.2 (− 4.5, − 2.0)***
Placebo	84	− 1.5 (− 2.1, − 0.8)***	76	− 0.8 (− 1.6, 0.0)	85	− 1.6 (− 2.8, − 0.3)**
Ravulizumab vs. placebo	168	− 1.1 (− 2.0, − 0.2)*	155	− 1.8 (− 3.0, − 0.6)**	170	− 1.6 (− 3.4, 0.2)
Week 26 (time of best response)						
Ravulizumab	78	− 3.1 (− 3.8, − 2.3)***	76	− 2.8 (− 3.7, − 1.9)***	78	− 3.3 (− 4.7, − 1.9)***
Placebo	82	− 1.4 (− 2.1, − 0.7)***	78	− 0.8 (− 1.7, 0.1)	82	− 1.6 (− 3.0, − 0.3)*
Ravulizumab vs. placebo	160	− 1.6 (− 2.6, − 0.7)**	154	− 2.0 (− 3.2, − 0.8)**	160	− 1.7 (− 3.4, 0.1)
MAIC results anchored on above comparisons with placebo						
Efgartigimod vs. ravulizumab at week 4	137	− 1.9 (− 3.3, − 0.5)**	131	− 3.2 (− 5.2, − 1.2)**	138	− 4.0 (− 6.6, − 1.4)**
Efgartigimod vs. ravulizumab at time of best response	131	− 1.4 (− 2.8, 0.0)*	128	− 3.0 (− 5.0, − 1.0)**	131	− 3.9 (− 6.5, − 1.3)**

AChR-Ab+ Acetylcholine Receptor Auto-antibodies Positive, *CI* Confidence Interval, *gMG* generalized Myasthenia Gravis, *MAIC* Matching-Adjusted Indirect Comparison, *MG-ADL* Myasthenia Gravis Activities of Daily Living, *MG-QoL15r* Myasthenia Gravis Quality of Life 15-item-revised scale, *QMG* Quantitative Myasthenia Gravis

*p value < 0.05; **p value < 0.01; ***p value < 0.001

Table 4 Relative effect of efgartigimod versus ravulizumab in terms of minimum points improvement from baseline at time of best response[a] for MG-ADL in people with AChR-Ab+ gMG derived using MAIC

	N	Proportion (95% CI) of patients with minimum points improvement in MG-ADL from baseline at time of best response		
		3 points	4 points	5 points
Adjusted results estimated using reweighted data from the ADAPT study				
Efgartigimod	53	0.752 (0.633, 0.871)***	0.681 (0.553, 0.809)***	0.610 (0.476, 0.744)***
Placebo	55	0.374 (0.241, 0.507)***	0.253 (0.133, 0.374)***	0.145 (0.048, 0.243)**
Efgartigimod vs. placebo	108	0.378 (0.200, 0.556)***	0.428 (0.252, 0.604)***	0.465 (0.296, 0.634)***
Results estimated from the CHAMPION study				
Ravulizumab	78	0.567 (0.456, 0.678)***	0.425 (0.314, 0.536)***	0.316 (0.211, 0.421)***
Placebo	82	0.341 (0.236, 0.446)***	0.247 (0.151, 0.343)***	0.150 (0.071, 0.229)**
Ravulizumab vs. placebo	160	0.226 (0.073, 0.379)**	0.178 (0.031, 0.325)*	0.166 (0.035, 0.297)*
MAIC results anchored on above comparisons with placebo				
Efgartigimod vs. Ravulizumab	131	0.152 (– 0.085, 0.388)	0.250 (0.019, 0.480)*	0.299 (0.085, 0.513)**

AChR-Ab+ acetylcholine receptor auto-antibody-positive, *CI* confidence interval, *gMG* generalized Myasthenia Gravis, *MAIC* Matching-Adjusted Indirect Comparison, *MG-ADL* Myasthenia Gravis Activities of Daily Living
*p value < 0.05; **p value < 0.01; ***p value < 0.001
[a]Week 4 for efgartigimod and week 26 for ravulizumab

– 2.3]; $p = 0.041$). There was not a statistically significant difference between efgartigimod and ravulizumab for MG-ADL (mean difference [95% CI] = – 8.7 [– 36.1, 18.8]; $p = 0.534$) or QMG (– 13.7 [– 50.3, 22.9]; $p = 0.464$) over 26 weeks.

Change from Baseline at Week 4 for MG-ADL, QMG and MG-QoL15r

Compared with placebo, in the adjusted MAIC population, efgartigimod achieved a statistically significant reduction in MG-ADL, QMG and MG-QoL15r from baseline at week 4 (Table 3). Ravulizumab also achieved a statistically significant reduction in MG-ADL and QMG at week 4, but not in MG-QoL15r, compared with placebo.

At week 4, compared with ravulizumab, efgartigimod was associated with greater improvement in MG-ADL (– 1.9 [– 3.3, – 0.5]; $p = 0.007$), QMG (– 3.2 [– 5.2, – 1.2]; $p = 0.001$), and MG-QoL15r (– 4.0 [– 6.6, – 1.4]; $p = 0.002$).

Change from Baseline at Time of Best Response for MG-ADL, QMG and MG-QoL15r

Compared with placebo, in the adjusted MAIC population, efgartigimod achieved a statistically significant reduction in MG-ADL, QMG and MG-QoL15r from baseline at time of best response (Table 3; week 4). Ravulizumab also achieved a statistically significant reduction in MG-ADL and QMG at week 26 (time of best response), but not in MG-QoL15r, compared with placebo.

Compared with ravulizumab, at the time of best response, efgartigimod was associated with greater improvement in MG-ADL (– 1.4 [– 2.8, – 0.0]; $p = 0.046$), QMG (– 3.0 [– 5.0, – 1.0];

$p = 0.003$), and MG-QoL15r (– 3.9 [– 6.5, – 1.3]; $p = 0.003$).

Minimum Point Improvements in MG-ADL from Baseline

The MAIC suggests that significantly more patients with efgartigimod than with ravulizumab experienced a minimum improvement of at least 4 and 5 points in MG-ADL from baseline at time of best response, with adjusted differences of 0.25 (95% CI 0.02, 0.48; $p = 0.033$) and 0.30 (0.09, 0.51; $p = 0.006$), respectively (Table 4). The proportion of patients with at least 3 points reduction in MG-ADL from baseline at time of best response was not statistically significantly different between efgartigimod and ravulizumab (0.15 [– 0.09, 0.39; $p = 0.207$).

NNT at Time of Best Response

After reweighting, the NNT for efgartigimod versus placebo was lower than the NNT for ravulizumab versus placebo to observe one additional patient with ≥ 3 (2.65 vs. 4.42 respectively), ≥ 4 (2.34 vs. 5.62 respectively), or ≥ 5 (2.15 vs. 6.02 respectively) points improvement in MG-ADL from baseline at time of best response. The difference between efgartigimod versus placebo and ravulizumab versus placebo was statistically significant for ≥ 4 ($p = 0.033$) and ≥ 5 ($p = 0.006$) points improvement. This implies that fewer patients need to be treated with efgartigimod than ravulizumab to achieve the same outcome.

DISCUSSION

Overall Findings

The findings of this ITC suggest that, although both treatments were effective, efgartigimod improved QoL (as measured by MG-QoL15r) to a greater extent than ravulizumab over 26 weeks. Additionally, efgartigimod was associated with greater improvements in MG-ADL (a measure of ability to conduct activities of daily living), QMG (a measure of muscle strength), and MG-QoL15r at 4 weeks and time of best response (4 weeks for efgartigimod and 26 weeks for ravulizumab). Finally, fewer patients would need to be treated with efgartigimod than ravulizumab to achieve the same response (measured on MG-ADL score) based on the NNT findings.

Interpretation of Results in Context of Other Literature

In AChR-Ab+ gMG, many patients remain symptomatic despite receiving treatment, therefore it is important to understand the comparative efficacy of new and existing treatment options. Despite this, there is no direct evidence in the literature comparing the efficacy of efgartigimod with ravulizumab in treating gMG. A recent analysis of treatments conducted by Saccà et al. in the wider condition of myasthenia gravis included efgartigimod, ravulizumab, and other therapies, and concluded that anti-complement therapies and neonatal Fc receptor blockers were both effective, with the network meta-analysis showing that efgartigimod had the highest probability of being the best treatment for MG-ADL (31.5%) and for QMG (62.6%) [12]. These findings expand on this previous work by focusing on patients with AChR-Ab+ gMG and using ITC methods that allow for better adjustment of population differences.

The primary analyses considered the first 26 weeks of treatment via AUC analyses, which allow measurement of the treatment effect over the entire observation period, rather than at a specific timepoint. The results showed that efgartigimod resulted in a greater cumulative improvement in MG-QoL15r compared with ravulizumab over the 26 week follow-up period. There was not a significant difference in MG-ADL or QMG between the two treatments over 26 weeks. These findings suggest that efgartigimod may have a benefit if treatment effects need to be achieved fast and if QoL is an important consideration for the patient, which is often the case given that it can severely impact gMG patients [2, 3]. This aligns with the treatment goals stated in the most recent

German treatment guidelines on myasthenic syndromes, which state: "Of essence is that the guidelines positions treatment goals as follows: The therapeutic goal is to achieve the best possible disease control while restoring the patient's quality of life (strong consensus)." [13].

Efgartigimod also appears to be at least as effective as ravulizumab when considering the cumulative change in measures of disease activity (MG-ADL and QMG) over the first 26 weeks of treatment, despite the cyclic treatment approach. Stringent retreatment criteria were applied in ADAPT [1], such that patients had to worsen considerably (MG-ADL of ≥ 5 and loss of clinically meaningful improvement in MG-ADL score) before they could be retreated, and that there was at least 8 weeks between cycles. Conversely, in real-life settings, there is no need to wait for worsening of symptoms before retreatment can begin, and no time limit between cycles (although there are no clinical trial data on the effectiveness or safety of initiating cycles sooner than 7 weeks), and instead retreatment can be based on clinical evaluation, which may further increase the AUC effect sizes.

In a comparison of change from baseline to 4 weeks versus placebo, efgartigimod was associated with statistically significant greater improvements than ravulizumab in MG-ADL, QMG, and MG-QoL15r. These results strongly suggest that efgartigimod confers a clinical benefit to patients with gMG faster than ravulizumab, as a significant difference is seen as early as 4 weeks. The ADAPT study also showed a fast response for efgartigimod, with a clinically meaningful improvement in MG-ADL as early as 1 week into treatment [1]. We speculate that the mode of action of efgartigimod may explain these findings. gMG is an autoimmune disease, mediated by IgG auto-antibodies, mainly AChR antibodies. These auto-antibodies exert three pathogenic effects: (1) functional block of AChR; (2) crosslinking and degradation of AChRs; and (3) antibody-mediated complement activation. Efgartigimod acts upstream, by reducing antibody levels, and impacts all three mechanisms.

Analyses of time of best response were conducted to reflect the different treatment schedules and modes of action of efgartigimod and ravulizumab to ensure as far as possible a like-for-like comparison. The time of best response may be greater than this, which could only be assessed via longer-term follow-up data. Based on the ADAPT and CHAMPION studies [1, 6], the time of best response was selected as 4 weeks for efgartigimod and 26 weeks for ravulizumab. This aligns with a network meta-analysis of treatments for myasthenia gravis [12]. In our comparison of change from baseline versus placebo, efgartigimod was associated with statistically significant greater improvement than ravulizumab in MG-ADL, QMG, and MG-QoL15r. These results imply that efgartigimod confers a greater clinical benefit to patients with gMG than ravulizumab at the time of best response. However, it is important to note that time of best response can only be defined over the 26-week study period for which data were available, and that the actual time of best response may be longer than this, particularly for ravulizumab. The Saccà et al. network meta-analysis similarly found that efgartigimod had the highest probability of being the best treatment in terms of MG-ADL (31.5%) and QMG (62.6%) [12].

Additionally, analyses on minimum point improvements and NNT for MG-ADL were conducted at the time of best response. These analyses found that significantly more patients with efgartigimod than with ravulizumab experienced ≥ 4 and ≥ 5 points improvement in MG-ADL from baseline at time of best response. This resulted in fewer patients needing treatment with efgartigimod than ravulizumab to achieve a ≥ 4 and ≥ 5 points improvement in MG-ADL, respectively. The findings for ≥ 3 points improvement were in the same direction (i.e., favored efgartigimod); however, they were not statistically significant.

Limitations and Future Research

Whilst ITC analyses allow comparison of treatments where no head-to-head studies exist, they have limitations, as described below. Therefore, a future randomized trial directly

comparing efgartigimod and ravulizumab should be performed.

A limitation of these analyses is related to the choice of the covariates included in the ITC. Following the NICE guidelines on adjusted ITC methods, evidence should be presented that there are grounds for considering one or more covariates as treatment effect modifiers. In the context of our analyses, the stratification variables (Japanese/non-Japanese ethnicity; receiving of non-steroidal immunosuppressive drug at baseline) used for the sub-group analyses in ADAPT were used as MAIC covariates, implicitly assuming that they were potential treatment effect modifiers. These were selected as their use within the ADAPT trial as stratification variables implies that they are likely confounders. However, no formal analysis or research was conducted to verify that the selected covariates were potential treatment effect modifiers or that the imbalance in the two trials was large enough to produce a significative difference in the estimated treatment comparison.

Other limitations relate to the different treatment schedules for efgartigimod and ravulizumab, which makes comparison between the two treatments difficult. In particular, selecting Timepoint for analyses was complex with no clear timepoint on which to base the comparison due to the different treatment schedules. Therefore, to address this, three different Timepoint were analyzed. Nevertheless, disregarding the difference at other Timepoint may result in an over- or underestimate of the efgartigimod effect versus ravulizumab. This limitation has also been highlighted by others [12]. The impact of this is likely to be limited, as the findings are consistent across the different analyzed Timepoint. Thus, indicating that the greater benefit estimated for efgartigimod versus ravulizumab on the different outcomes is likely not an overestimation of effect.

CONCLUSION

These findings suggest that efgartigimod induces a faster and deeper quality of life response than ravulizumab in people with AChR-Ab+ gMG, and that, over 26 weeks, this is retained to an acceptable extent over the off-treatment period associated with the efgartigimod treatment schedule.

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Data Availability. The datasets generated during and/or analyzed during the current study are not publicly available due to commercial sensitivity.

Declarations

Conflict of Interest. Cécile van Steen and Sergio Iannazzo were employees of argenx BV, who manufacture efgartigimod, when the manuscript was completed. Cécile van Steen has since changed affiliation to Biogen Netherlands BV. Celico, Spaepen, Bodicoat and de Francesco have received research funding from argenx BV. Hagenacker has received research support from Biogen, Novartis GeneTherapies, Roche and Sanofi Genzyme, speakers and consultant honoraria from Biogen, Hormosan, Roche, Alexion, Novartis, Roche, Sanofi-Genzyme, Alnylam and Argenx. Sven G. Meuth received honoraria for lecturing and travel expenses for attending meetings from Almirall, Amicus Therapeutics Germany, Bayer HealthCare, Biogen, Celgene, Diamed, Genzyme, MedDay Pharmaceuticals, Merck Serono, Novartis, Novo Nordisk, ONO Pharma, Roche,

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Ethical Approval. This article is based on previously conducted studies and does not contain any new studies with human participants or animals performed by any of the authors, therefore IRB approval was not required. In this indirect treatment comparison, no real-life patients were included and IRB approval was therefore not required.

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