Symptomatic treatment of myasthenia gravis and its role in the era of emerging immunomodulatory treatments

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CHAPTER

4

Efficacy and cost-utility of pyridostigmine

Efficacy of pyridostigmine in myasthenia gravis:
a randomized, double-Blind, placebo-controlled crossover trial

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Abstract

Background and objectives

Pyridostigmine, an acetylcholinesterase inhibitor, is a symptomatic drug approved for the treatment of myasthenia gravis (MG), but no randomized controlled trials substantiate its widespread use. We aimed to assess the efficacy and cost-utility of pyridostigmine in patients with anti-acetylcholine receptor positive MG (AChR MG).

Methods

A randomized, double-blind, placebo-controlled crossover trial was conducted at Leiden University Medical Center, a tertiary center for the treatment of MG in the Netherlands. Main eligibility criteria were current use of pyridostigmine, and a stable dose of other MG treatments. Participants were assigned to a sequence of two treatment periods for five days separated by a two-day washout, in which patients either first received placebo and then pyridostigmine, or vice versa. Pyridostigmine dosing matched each participant's pre-study regimen. The primary outcome was change in Myasthenia Gravis Impairment Index (MGII) score. Secondary efficacy outcome measures included the Myasthenia Gravis-Activities of Daily Living (MG-ADL) scale, the Quantitative Myasthenia Gravis (QMG) score and the revised 15-item Myasthenia Gravis Quality of Life (MG-QOL15r) questionnaire. For the post hoc cost-utility analysis, a mathematical model was developed to translate the observed study results into long-term annual impact on societal costs and quality-adjusted life-years (QALYs).

Results

Nineteen patients (median age 59 years, 58% female) were recruited between March 23, 2023 and February 21, 2024. The estimated mean difference between pyridostigmine and placebo was 5.3 for MGII score (95% confidence interval [CI] 1.9-8.7, p=0.004). Secondary efficacy outcome measures showed estimated mean differences of 1.4 (95% CI 0.5-2.3) for QMG-score, 1.2 (95% CI 0.5-1.8) for MG-ADL-score, and 2.0 (95% CI 0.03-3.91) for MG-QoL15r-score. The post hoc cost-utility analysis showed lower annual societal costs (€6565, 95% CI €328-€15945), and annual improved QALYs (0.106, 95% CI 0.019-0.210) for patients using pyridostigmine.

Discussion

This trial showed that in patients with AChR MG chronically using pyridostigmine, pyridostigmine demonstrated benefit over placebo across all efficacy outcome measures and substantially reduced societal costs.

Introduction

Myasthenia gravis (MG) is a chronic autoimmune disease of the neuromuscular junction in which autoantibodies bind to the acetylcholine receptor (AChR) or other target proteins on the postsynaptic membrane, resulting in impairment of neuromuscular transmission. The main clinical features are weakness and fatigability in ocular, bulbar, limb and respiratory muscles.

Pyridostigmine is considered the first drug of choice in the treatment of MG and remains the cornerstone in the management of MG since its first introduction almost eighty years ago,[25,142] despite the recent introduction of new immunomodulatory drugs.[39] Pyridostigmine blocks the degradation of the neurotransmitter acetylcholine by inhibiting the enzyme acetylcholinesterase (AChE), which is responsible for hydrolyzing acetylcholine. As a result, pyridostigmine prolongs the duration of activity of acetylcholine in the synaptic cleft, thereby enhancing neuromuscular transmission.[143]

Formal recommendations on treatment with pyridostigmine suffer from a lack of evidence from randomized trials and rely solely on anecdotal data from case reports, case series, and clinical experience.[26,142] A 2014 Cochrane review concluded that, despite the absence of adequate randomized controlled trials, the clear effect of AChE inhibitors found in observational studies support their widespread use in the treatment of MG. However, these observational studies primarily assessed short-term effects of not only pyridostigmine, but also of neostigmine or edrophonium, which have a more rapid onset. Moreover, these studies were conducted prior to the advent of immunosuppressive therapies such as corticosteroids and azathioprine. Consequently, there is a lack of data on the long-term efficacy of AChE inhibitors, especially when used alongside modern immunosuppressive treatments. Given that over 60% of MG patients use pyridostigmine,[79] usually in combination with one of the many immunosuppressive agents, a critical evaluation of its role is warranted.

In addition to assessing the efficacy of pyridostigmine, it is essential to evaluate its cost-utility. In recent years, the advent of novel, but very costly immunomodulatory drugs has brought renewed focus on the cost-effectiveness of treatments for MG. Limited data on the cost-effectiveness of these emerging therapies are available,[144-146] and these studies mostly estimate utilities using proxy measures, such as QMG scores, rather than directly observed values. This limitation hampers the development of rational and cost-effective treatment strategies.

In IMPACT-MG, a randomized, double-blind, placebo-controlled crossover study, we aimed to investigate the efficacy, tolerability, and cost-utility of pyridostigmine in patients with AChR MG. The primary research question being addressed in this study was whether pyridostigmine improves MG symptoms compared with placebo, in patients on stable standard of care therapy and currently using pyridostigmine.

Methods

Study design and participants

IMPACT-MG was a two-part, investigator-initiated, prospective, randomized, double-blind, placebo-controlled crossover study of the efficacy, tolerability and cost-utility of pyridostigmine (part one) and pyridostigmine plus amifampridine combination therapy (part two). The results of part two will be published separately. The study was performed at Leiden University Medical Center, a tertiary center for the treatment of MG in the Netherlands.

Patients were eligible for the study if they were at least 18 years of age and had a documented diagnosis of ocular or generalized MG with evidence of elevated AChR antibodies. A maximum of five patients with purely ocular MG were included, to ensure that the study population accurately reflected the clinical population. Eligibility required a Myasthenia Gravis Foundation of America (MGFA) clinical classification of class I to IV at screening,[147] current use of pyridostigmine, and a stable dose of other MG treatments. Stability was defined as follows: at least one month on a stable steroid regimen; at least three months since initiating azathioprine, mycophenolate mofetil, cyclosporine or other nonsteroid immunosuppressive agents with a stable dose for at least one month; at least six months since starting rituximab, complement inhibitors or Fc receptor inhibitors with a stable dose for at least three months for the latter two. Patients were excluded from the trial if they had a history of thymectomy within the six months before screening, or thymectomy (expected) to take place during the trial, had used intravenous immunoglobulin (IVIg) or undergone plasma exchange (PLEX) in the last four weeks preceding the trial or planned to do so during the study, or were currently using AChE inhibitors other than pyridostigmine, including pyridostigmine slow-release. A full list of inclusion and exclusion criteria is provided in the supplementary material.

Potential patients were recruited from the investigators' practice, through the Dutch neuromuscular patient organization "Spierziekten Nederland", or through the existing newsletter for participants in the Dutch MG registry.

Randomization and masking

Eligible participants were randomly assigned (1:1) to one of two treatment groups, in which patients either first received placebo and then received pyridostigmine, or vice versa. Randomization was done with the Castor Electronic Data Capturing System (Castor EDC; Amsterdam, the Netherlands) using variable block sizes (two, four and six patients), without any stratification. The pyridostigmine 10 mg and placebo tablets appeared identical to maintain the double-blinding and were dispensed by the hospital pharmacy and distributed in identical blister packs. Only tablets of 10 mg were used, since the 60 mg tablets have a coating color that could not be identically reproduced for the placebo. All study personnel

(except the study pharmacist) and all participants remained masked to the allocation sequence until after the study database lock. The efficacy of blinding was assessed by asking the investigator and the patient which treatment they believed the patient had received in the past week.

Study procedures

After consent was obtained, screening assessments were performed and patients were instructed to stop their regular use of pyridostigmine for a two-day washout period. Patients who were unable to complete this two-day washout period were excluded from participating in part one of the study. Patients were randomly assigned to a sequence of two treatment periods for five days separated by a second two-day washout. The dose of pyridostigmine was set at the therapeutic dose of pyridostigmine as determined before inclusion in clinical routine care based on patient response and tolerance. The dosing schedule of placebo was the same as that of the active treatment. Patients were allowed to prematurely discontinue treatment and resume their prior pyridostigmine regimen if they experienced a compelling need to alleviate MG symptoms. Before initiation of rescue pyridostigmine treatment, primary, secondary and tolerability parameters were assessed by the investigator.

Throughout the trial, patients were required to maintain the same dosage and treatment schedule for oral corticosteroids, and other immunosuppressive treatments as before inclusion in the trial.

For evaluation of efficacy, we assessed the following validated outcome measures: the MGII [148], the Myasthenia Gravis-Activities of Daily Living (MG-ADL) scale,[149] the Quantitative Myasthenia Gravis (QMG) score,[150] and the revised 15-item Myasthenia Gravis Quality of Life (MG-QOL15r) questionnaire.[151] Treatment satisfaction was evaluated using the 9-item Treatment Satisfaction Questionnaire for Medication (TSQM-9).[152] MGII was assessed at screening, baseline (day 1, pre-treatment), day 5 and day 12. MG-ADL, QMG, and MG-QOL15r were scheduled at baseline, day 5 and day 12. TSQM-9 was assessed at day 5 and day 12.

Patients were actively asked for adverse events during each visit and the severity of these events was assessed. To assess tolerability, side effects were evaluated using a questionnaire that was previously developed to assess the side effects of pyridostigmine in a cross-sectional study.[79] A full list of the side effects queried is shown in the supplementary material.

Laboratory testing at baseline and day 12 included a blood cell count, assessment of electrolytes, renal function, liver enzymes, creatine kinase and AChR antibody titers. In addition, serum concentrations of pyridostigmine were collected at each visit.

For the economic evaluation, to measure health-related quality of life, the 5-level EuroQol 5 Dimensions (EQ-5D-5L) and the EuroQol's visual analogue scale (EQ-VAS) were obtained at baseline, day 5 and day 12.[153] Prior healthcare use and productivity were assessed at baseline using the Medical Technology Assessment (iMTA) Medical Consumption

Questionnaire (iMCQ),[154] and the iMTA Productivity Cost Questionnaire (iPCQ).[155] The iMCQ was modified by omitting the modules related to medication and travel, and the recall periods for the iMCQ and iPCQ were set to 12 and 3 months, respectively.

Outcome measures

The primary efficacy outcome was a mean clinically meaningful difference in MGII total score while using pyridostigmine compared to placebo. A change of ≥8 is considered a clinically meaningful improvement.[156] The MGII was chosen as the primary outcome measure because it provides a broader range of scores and has less floor effect compared to other commonly used outcome measures.[148]

Prespecified secondary efficacy endpoints were mean clinically meaningful changes on the MG-ADL scale, the QMG score, the MG-QOL15r questionnaire, the MGII ocular and generalized subscores, and the TSQM-9. A clinically meaningful improvement was defined as a 2-point change in the MG-ADL score,[157] and a 3-point change in the QMG score.[150] Tolerability and safety outcomes were incidences of adverse events, side effects, and vital signs. Treatment adherence was assessed by use of a diary and via pill counts of returned study medication.

Economic evaluation

The economic evaluation consisted of a cost-utility analysis from a societal perspective. Main outcomes were the differences in costs, quality-adjusted life years (QALYs) and net benefit between the policies with and without pyridostigmine.

Utilities were calculated from the EQ-5D-5L responses using the Dutch tariff.[158] Utilities reflect the value of quality of life on a scale anchored at 0 (= as bad as death) and 1 (= full health). EQ-VAS scores were transformed to a utility scale using the power transformation 1 - (1 - EQ-VAS/100)^1.61.[159] All healthcare costs were calculated as reported in the iMCQ and valued according to Dutch guidelines for economic healthcare evaluations, using Dutch unit reference prices and including travel costs.[160] Standard prices for medication were obtained from the database provided by the National Health Care Institute.[161] Productivity costs were estimated from the number of workdays lost due to absenteeism and work cutback (presenteeism) as reported in the iPCQ questionnaire. Productivity losses were valued using the human-capital method, at €43.44 per hour for paid labor and €20.48 for unpaid labor.[160] Societal costs were calculated as the sum of healthcare costs, including medication, and productivity costs. All costs are reported in Euros and all prices were indexed to 2024 using the Dutch consumer price index.

Since the time horizon of the current clinical trial was five days for each treatment period, a mathematical model was needed to extrapolate the observed short-term trial results to the impact on societal costs and QALYs for a long-term one-year period. This impact was

predicted from correlations in the baseline measurements. First, linear regression and logistic regression models on the baseline data were used to estimate (1) the impact of corticosteroid use on EQ-5D and EQ-VAS utility scores using a linear regression model, (2) the probability of long-term corticosteroid use based on the MGII using a logistic regression model, and (3) the impact of MGII, utility according to the EQ-5D and EQ-VAS, and corticosteroid use on overall costs using a linear regression model.
Next, these regression models were used to translate the observed short-term impact on MGII and utility scores to long-term annual outcome. The modelled total long-term impact on QALYs consisted of the directly observed short-term difference in EQ-5D utility scores, minus the long-term probability of corticosteroid use (as predicted by the logistic regression) times the disutility due to corticosteroid use (as predicted by the linear regression model for utility). The modelled total long-term impact on societal costs consisted of the medication costs, plus other healthcare and non-healthcare costs (as predicted by the linear regression models for costs and the logistic regression for corticosteroid use). Finally, the differences in QALYs and costs were combined using net-benefit analysis. The willingness-to-pay (WTP) among MG patients was based on the recommendations of the National Health Care Institute with a value of €20,000 per QALY for conditions with limited burden of disease.[162] Cost-effectiveness acceptability curves (CEACs) were used to estimate the probability that pyridostigmine is cost-effective compared to placebo. Overall sampling uncertainty was incorporated using non-parametric bootstrapping, taking 1000 resamples and applying the entire process of regression models and calculations to each sample. We used a bias-corrected and accelerated approach to calculate confidence intervals. Two sensitivity analyses were performed: (1) applying a healthcare instead of societal perspective and (2) using QALYs estimated from the EQ-VAS instead of the EQ-5D (thus taking the patients' perspective on health instead of the societal perspective).

Statistical analysis

Based on previous data with similar populations of MG patients,[156,163,164] a sample size of 17 participants was expected to have 90% power to detect a difference of 8 points on the MGII with a two-sided p value of 0.05. We assumed the standard deviation of repeated measurements of MGII between patients to be 13 and the intraparticipant correlation to be 0.7.[156,163,164] Allowing for a 10% drop out rate, we aimed to include 19 patients.
No interim statistical analyses were conducted, and no adaptations to the study design were planned or performed. Descriptive statistics were used to summarize baseline characteristics, presented as means and standard deviations (SDs) or medians and interquartile ranges (IQRs). Primary analysis was performed according to the intention-to-treat principle. A mixed-effects linear regression model was used to analyze repeated measures and estimate least-square mean differences between pyridostigmine and placebo, with treatment and treatment period (categorical) as fixed factors and patients as a random effect. The same

model was applied to secondary and exploratory outcomes. Statistical significance was determined by a p-value less than 0.05.
All statistical analyses were predefined in the study protocol. No data were missing for the primary outcome analyses and no data imputation was performed to account for missing data. All statistical analyses were conducted using RStudio (version 4.4.0).

Results

Fifty-five patients were screened for eligibility between March 22, 2023, and Feb 21, 2024, of whom 18 patients did not meet eligibility criteria, and 16 patients declined participation. Two patients failed to complete the washout period prior to randomization and were therefore excluded from participation in part one. Nineteen patients were enrolled and randomly assigned to receive either first pyridostigmine and then placebo (n=10) or vice versa (n=9); **Figure 4.1**. Two participants resumed pretrial pyridostigmine treatment prematurely on day 10 since randomization (in which the treatment was placebo) due to an intolerable increase in MG symptoms. In both patients, the primary and secondary outcome measures were determined before the pretrial medication was resumed. All 19 randomly assigned participants were included in the primary and secondary analyses.
Patient demographics and baseline characteristics are summarized in **Table 4.1**. Patients predominantly had mild to moderate generalized MG at baseline, with a small proportion of patients presenting with ocular symptoms only, according to the MGFA disease classification criteria.
Healthcare costs and non-healthcare costs in the year before inclusion are summarized in **Supplementary Table 4.1** and **Supplementary Table 4.2**, respectively. The interaction between corticosteroid use and the MGII score at baseline is shown in **Supplementary Figure 4.1**.

Table 4.2 provides the least square mean values during placebo treatment, and during pyridostigmine treatment, as well as the placebo-pyridostigmine treatment difference, for the primary and secondary outcome variables. The mean treatment difference in MGII total score between pyridostigmine and placebo (primary endpoint) was -5.3 points (95% CI -8.7, -1.9); p = 0.004). The least square mean values for the MGII total score were 32.0 (95% CI 24.9-39.2) with placebo, and 26.7 (95% CI 19.6-33.9) with pyridostigmine. Statistically significant differences were also observed across all secondary efficacy outcome measures, including MGII ocular, MGII generalized, QMG, and MG-ADL, quality of life (MG-QoL15r), and treatment satisfaction (TSQM-9). There was no evidence of a treatment-by-period interaction (**Supplementary Table 4.3**).

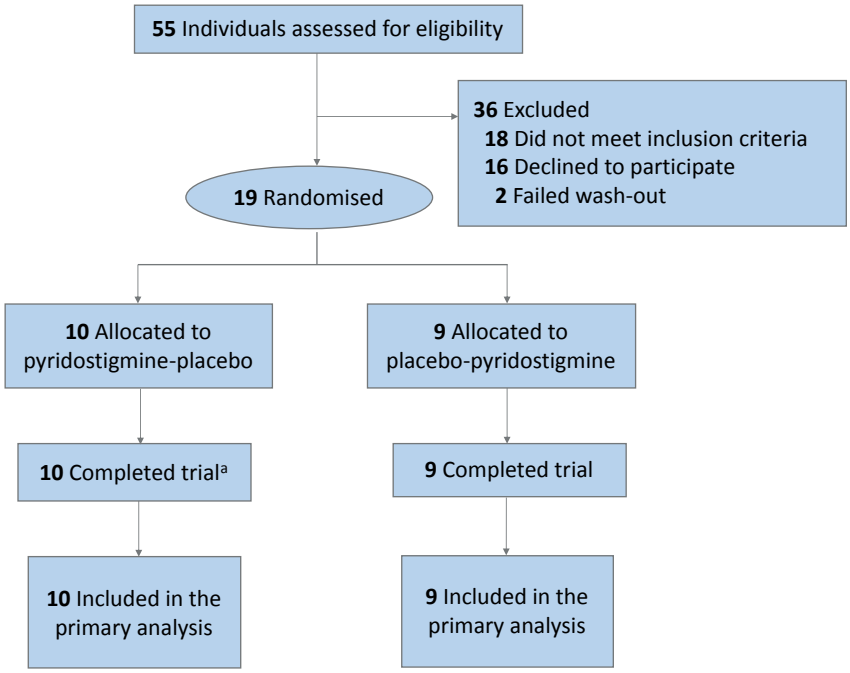


Figure 4.1 Flow diagram
[a] In two patients, primary and secondary outcome measures were obtained prematurely due to an intolerable increase in MG symptoms during the placebo treatment week.

Figure 4.2 shows the absolute values for each participant at baseline and during treatment with pyridostigmine and placebo for the MGII and EQ-5D utility score. **Supplementary Figure 4.2** presents the corresponding values for the remaining secondary outcome measures. Treatment adherence was excellent with 99% compliance with dosing (doses taken per doses scheduled) during both pyridostigmine and placebo treatment.

The number of participants who correctly guessed their treatment allocation in the preceding period was 13 (68%) during pyridostigmine treatment and 16 (84%) during placebo treatment. The investigators correctly guessed the treatment allocation in 14 participants (74%) during pyridostigmine treatment and in 17 participants (89%) during placebo treatment.
Side effects are shown in **Table 4.3**. Twelve participants (63%) reported at least one side effect during treatment with pyridostigmine, compared to 7 participants (37%) during treatment with placebo. No serious adverse events occurred in any patients during the

study. Pulse rates were lower during treatment with pyridostigmine (least square mean 70.4 [95% CI 65.3-75.5]) compared with placebo (least square mean 74.6 [95% CI 69.5-79.7], p=0.003). There was no statistically significant difference between pyridostigmine and placebo in blood pressure and respiratory rate. Results of laboratory testing and serum concentrations of pyridostigmine are shown in **Supplementary Table 4.4** and **4.5**, respectively.

Table 4.1 Baseline characteristics

	Overall, N = 19	**Pyridostigmine then placebo, N = 10**	**Placebo then pyridostigmine, N = 9**
Age, years	59 (39, 69)	60 (43, 64)	58 (36, 69)
Age at onset, years	49 (26, 60)	37 (19, 57)	53 (36, 65)
Sex, female	11 (58%)	8 (80%)	3 (33%)
BMI, kg/m2	28.2 (25.9, 28.7)	28.3 (26.5, 28.6)	26.4 (25.5, 28.7)
Disease duration, years	6 (2, 16)	13 (6, 23)	4 (2, 5)
Previous thymectomy, yes	7 (37%)	4 (40%)	3 (33%)
MGFA score at inclusion			
I	3 (16%)	2 (20%)	1 (11%)
II	14 (74%)	6 (60%)	8 (89%)
III	2 (11%)	2 (20%)	0 (0%)
Total daily dose pyridostigmine (mg)	240 (190, 300)	240 (185, 300)	250 (240, 300)
Baseline scores			
MGII total	26 (23, 36)	27 (25, 37)	24 (22, 32)
QMG	11 (9, 15)	12 (9, 15)	10 (7, 14)
MG-ADL	6 (4, 9)	7 (5, 10)	4 (3, 9)
MG-QoL15r	12 (9, 15)	13 (10, 16)	10 (9, 15)
Economic characteristics			
Utility, EQ-5D	0.77 (0.65, 0.86)	0.79 (0.62, 0.83)	0.77 (0.69, 0.91)
Utility, EQ-VAS	0.82 (0.69, 0.90)	0.80 (0.68, 0.88)	0.84 (0.77, 0.90)
Therapies in previous year			
No therapy	9 (47%)	4 (40%)	5 (56%)
Prednisolone	7 (37%)	4 (40%)	3 (33%)
Azathioprine	2 (11%)	2 (20%)	0 (0%)
Mycophenolate mofetil	4 (21%)	2 (20%)	2 (22%)
Cyclosporine	1 (5.3%)	0 (0%)	1 (11%)
Methotrexate	1 (5.3%)	1 (10%)	0 (0%)
IVIg on a regular basis	1 (5.3%)	1 (10%)	0 (0%)

Data are median (Q1-Q3) or n (%).
BMI, Body Mass Index; MGFA, Myasthenia Gravis Foundation of America; MGII, Myasthenia Gravis Impairment Index; QMG, Quantitative Myasthenia Gravis; MG-ADL, Myasthenia Gravis-Activities of Daily Living; MG-QoL15r, revised 15-item Myasthenia Gravis Quality of Life; EQ-5D, EuroQoL-5 dimensions; EQ-VAS, EuroQoL-visual analogue scale; IVIg, intravenous immunoglobulin therapy

Table 4.2 Treatment difference on primary and secondary outcome variables

	Pyridostigmine (95% CI)[a]	Placebo (95% CI)[a]	Difference (95% CI)[a]	P-value
Primary outcome				
MGII total	26.7 (19.6, 33.9)	32.0 (24.9, 39.2)	-5.3 (-8.7, -1.9)	0.004
Secondary outcomes				
MGII ocular	10.0 (6.9, 13.2)	12.4 (9.3, 15.5)	-2.4 (-4.2, -0.6)	0.012
MGII generalized	16.7 (10.7, 22.6)	19.6 (13.6, 25.5)	-2.9 (-5.4, -0.5)	0.023
QMG	10.5 (7.8, 13.2)	11.9 (9.2, 14.6)	-1.4 (-2.3, -0.5)	0.005
MG-ADL	5.9 (4.2, 7.6)	7.0 (5.4, 8.7)	-1.2 (-1.8, -0.5)	0.001
MG-QoL15r	11.4 (8.4, 14.4)	13.4 (10.3, 16.4)	-2.0 (-3.9, 0.0)	0.047
TSQM-9	35.8 (32.4, 39.1)	28.5 (25.2, 31.9)	7.2 (2.3, 12.2)	0.006

[a] Values are least square means from a mixed effects linear model that includes a fixed effect for treatment period and a random effect for participant. CI, confidence interval; MGII, Myasthenia Gravis Impairment Index; QMG, Quantitative Myasthenia Gravis; MG-ADL, Myasthenia Gravis-Activities of Daily Living; MG-QoL15r, revised 15-item Myasthenia Gravis Quality of Life; TSQM-9, 9-item Treatment Satisfaction Questionnaire for Medication

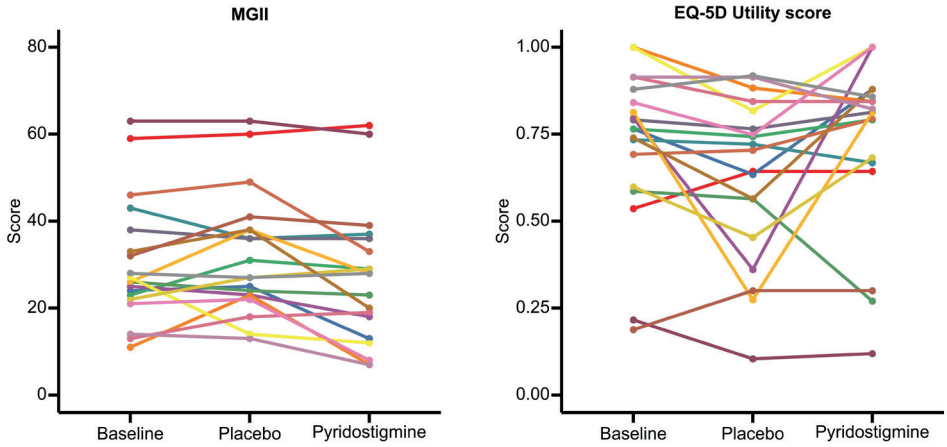


Figure 4.2 Absolute values for each participant at baseline and during treatment with pyridostigmine and placebo for the MGII and EQ-5D utility score
MGII, Myasthenia Gravis Impairment Index; EQ-5D, EuroQoL-5 dimensions.

Table 4.3 Summary of side effects in all patients

	Pyridostigmine	Placebo
Number of reported side effects	68	36
Patients having at least one side effect	12 (63%)	7 (37%)
Flatulence	7 (37%)	2 (11%)
Fatigue	6 (32%)	6 (32%)
Increased lacrimation	5 (26%)	3 (16%)
Urinary urgency	5 (26%)	2 (11%)
Increased salivation	5 (26%)	2 (11%)
Muscle weakness	4 (21%)	5 (26%)
Diarrhea	4 (21%)	1 (5%)
Muscle twitching	4 (21%)	1 (5%)
Light-headedness	3 (16%)	2 (11%)
Muscle cramps	3 (16%)	1 (5%)
Hot flushes	3 (16%)	0 (0%)
Flu-like symptoms	3 (16%)	0 (0%)
Nausea	2 (11%)	2 (11%)
Headache	2 (11%)	1 (5%)
Blushing	2 (11%)	1 (5%)
Abdominal cramps	2 (11%)	0 (0%)
Stomach ache	2 (11%)	0 (0%)
Increased bronchial secretion	1 (5%)	2 (11%)
Heartburn	1 (5%)	1 (5%)
Hyperhidrosis	1 (5%)	1 (5%)
Blurred vision	1 (5%)	1 (5%)
Irregular heartbeat	1 (5%)	1 (5%)
Slow heartbeat	1 (5%)	0 (0%)
Tremor	0 (0%)	1 (5%)

Data are number of patients (%) with one or more side effect. Excessive belching, vomiting, chest pain, skin rash, hives, and fainting were queried but not reported in either treatment period.

Table 4.4 provides the mean health economic outcomes during treatment with and without pyridostigmine, as well as the treatment difference. The cost-utility analysis showed lower annual societal costs (-€6565 [95% CI -€15945-€328]) with pyridostigmine treatment. Treatment with pyridostigmine resulted in more EQ-5D QALYs than without pyridostigmine (mean difference 0.106 [95% CI 0.019-0.210]). The cost-effectiveness plane showed that the majority of bootstrap points were located in the lower right quadrant (95.2%), indicating that treatment with pyridostigmine offers greater benefits at lower costs than treatment without pyridostigmine. The CEAC demonstrated a high probability (at least 99%) of pyridostigmine being cost-effective compared to placebo, at the €20000 per QALY threshold and higher (**Figure 4.3**). Sensitivity analyses resulted in different point estimates without altering the overall conclusion. In particular, the CEAC showed almost indistinguishable curves (**Supplementary Figure 4.3**).

Table 4.4 Estimated annual health and economic outcomes of treatment with and without pyridostigmine

	With pyridostigmine	Without pyridostigmine	Difference (95% CI)
QALYs based on EQ-5D	0.735	0.629	0.106 (0.019, 0.210)
QALYs based on EQ-VAS	0.761	0.690	0.071 (0.029, 0.125)
Long-term prednisolone use (%)	20.8	22.2	-1.4 (-13.8, 4.2)
Annual prednisolone costs (€)	7	8	-1 (-10, 2)
Annual pyridostigmine costs (€)	341	0	341 (283, 389)
Other annual healthcare costs (€)	6864	11398	-3821 (-12463, -395)
Total annual non-healthcare costs (€)	4662	7032	-1998 (-6987, 1389)
Total annual societal costs (€)	11871	18436	-6565 (-15945, 328)

Outcomes are based on non-parametric bootstrapping with 1000 replications.
QALYs, quality-adjusted life years; EQ-5D, EuroQoL-5 dimensions; EQ-VAS, EuroQoL-visual analogue scale

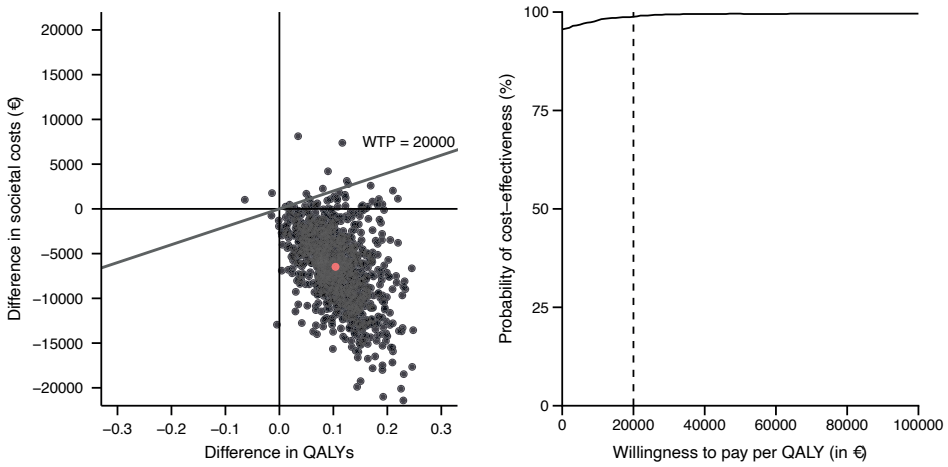


Figure 4.3 Cost−effectiveness results for the outcome of QALY, based on the societal perspective
Cost-effectiveness plane (left) and cost-effectiveness acceptability curve (right) of difference in QALYs derived from EQ-5D versus societal costs. Outcomes are based on non-parametric bootstrapping with 1000 replications.
QALYs, quality-adjusted life years; EQ-5D, EuroQoL-5 dimensions; EQ-VAS, EuroQoL-visual analogue scale; WTP, willingness to pay

Discussion

In IMPACT-MG, a randomized, double-blind, placebo-controlled crossover trial in patients with AChR myasthenia gravis chronically using pyridostigmine, we demonstrated that pyridostigmine was associated with improvements in the primary outcome measure (MGII -5.3 points) and all secondary outcome measures (MGII ocular -2.4 points, MGII generalized

-2.9 points, QMG -1.4 points, MG-ADL -1.2 points, MG-QoL15r -2 points, and TSQM-9 7.2 points) when compared to placebo. Adverse events were reported more frequently during the use of pyridostigmine in our study, with fatigue and flatulence being the most commonly reported. In the cost-effectiveness analysis, treatment with pyridostigmine was less costly and more effective than treatment without pyridostigmine. It showed a high probability of being cost-effective at a QALY threshold of €20,000, both from a societal and a healthcare perspective.

The observed mean difference for the primary outcome measure, the MGII, was below the predefined threshold for a clinically meaningful change. However, the 95% confidence interval included values that exceed this threshold, indicating that a clinically meaningful difference cannot be excluded. For the secondary efficacy outcomes, the QMG and the MG-ADL, pyridostigmine was also associated with statistically significant improvements. In contrast to the MGII, the predefined thresholds for clinically meaningful change on these outcomes fell outside the corresponding 95% confidence intervals. For the MG-ADL this may be (in part) explained by its well-known floor effect.[148] As many patients already had relatively low baseline scores, the potential for a measurable improvement was limited. This was one of the reasons why we selected the MGII as the primary outcome measure rather than the more commonly used MG-ADL. In addition, when interpreting whether the observed statistically significant differences are also clinically meaningful, it is important to consider that the thresholds for clinically meaningful improvement depend on the clinical and treatment context in which they were developed. For the MGII and QMG, these thresholds were developed in populations receiving treatments such as prednisone, IVIg, and PLEX,[156,165] which are more invasive and often associated with more severe adverse effects than pyridostigmine. It is likely that patients weigh the risks and side effects of these treatments when judging the minimal size of a beneficial effect. Consequently, a clinically meaningful improvement with a symptomatic treatment like pyridostigmine would be expected to be smaller than with these more invasive treatments. This suggests that cut-off values for a clinically meaningful improvement, developed in the context of immunomodulating therapies, may not be appropriate in trials investigating symptomatic medications. When comparing the results of our trial to other symptomatic treatments, such as the adrenergic agonist ephedrine or the ClC-1 inhibitor NMD670, the improvements demonstrated in these trials show similar effect sizes of respectively 1.0 and 1.5 points on the mean QMG score, comparable to 1.4 points in our study.[31,166] A study using terbutaline reports that 5 out of 8 patients had an improvement of more than 3 points on the QMG, while the other 3 patients had larger or unchanged QMG scores. This study did not provide the mean group values.[112]

One of the main strengths of our study is that, in addition to efficacy outcome measures, we included an analysis of the cost-effectiveness of pyridostigmine. Although pyridostigmine has been widely used for many years, assessing its cost-effectiveness remains particularly

important in an era of rising healthcare costs. While its cost-effectiveness cannot be directly compared to the effect of novel treatments, our data can serve as a benchmark for evaluating the cost-effectiveness of newer therapies. Moving forward, it is essential to include cost-effectiveness data when reporting efficacy outcomes for novel treatments, as this will provide a more comprehensive perspective on their value. Other strengths of our trial include the robust study design, consisting of a randomized, double-blinded, placebo-controlled crossover study, and the use of a wide range of both patient-reported and investigator-reported outcome measures, which effectively capture the impact of MG on patients and enable meaningful translation of results into clinical practice. Other strengths include the absence of drop-outs and the completeness of data for primary (100%) and secondary outcome measures (>99%).

Our study has some limitations. We only included patients who were currently using pyridostigmine, excluding those who had discontinued the medication or were treatment-naïve. Additionally, patients who could not tolerate the two-day washout period due to worsening of MG symptoms were excluded. Ideally, we would have selected recently diagnosed, untreated MG patients, however, this was not feasible, as identifying such patients would likely have required a multicenter, possibly multinational, trial, and it would have been ethically unacceptable to withhold treatment from untreated patients, even briefly. Although tapering pyridostigmine is common once patients are stable, some participants may not have required pyridostigmine during the trial. These factors should be considered when extrapolating our findings on efficacy to the general MG population.

The same considerations apply when evaluating tolerability. By including only patients currently using pyridostigmine, we may have selected patients with relatively few side effects, potentially leading to an overestimation of its tolerability. However, the trial data align well with a previous cross-sectional study in 410 MG patients on the effectiveness and side effects of pyridostigmine.[79]

Another limitation is the short treatment duration, which was based on the ethical decision that withholding ongoing pyridostigmine treatment from patients for a longer period was undesirable. Furthermore, a five-day treatment period was considered sufficient to adequately demonstrate the efficacy of pyridostigmine on MG symptoms compared to placebo, due to its rapid onset of action, but may have limited the likelihood of detecting infrequent adverse events. Most patients and investigators correctly identified the treatment allocation under blind conditions, potentially due to either a clear therapeutic effect or noticeable side effects. This may have introduced bias into the trial due to partial unblinding.

Several limitations related to the cost-effectiveness analysis should be noted. First, the cost-effectiveness analysis was not pre-specified as an outcome measure for this part of the study. Second, results may not be representative for other non-Dutch healthcare settings. Finally, the follow-up period was too short to directly observe the impact on healthcare use

and costs. Instead, these were extrapolated using cross-sectional baseline models, in which the estimated relationships do not need to be causal. For example, we predicted the use and impact of corticosteroid use from our baseline data, assuming that the observed cross-sectional relationships between the efficacy outcome measures and corticosteroid use were causal. In real-life, this relation is probably more complex. More accurate estimates for corticosteroid use could have been obtained from other larger data sets, however, for internal consistency, we chose to estimate all model components from our own trial data. Fortunately, the results showed that corticosteroid use had very little impact on the estimated outcomes. There is no guarantee that this also holds true for other parts of the economic model.

Conclusion

Our study demonstrated that treatment with pyridostigmine was associated with statistically significant improvements on efficacy scores, quality of life, and treatment satisfaction in patients with AChR MG chronically using pyridostigmine. In addition, pyridostigmine had a very high probability of being cost-effective at established willingness-to-pay thresholds, both from a societal and a healthcare perspective. The results from this study help define the current therapeutic landscape for patients with MG and the positioning of novel treatments with respect to finding a balance between the effectiveness, tolerability, and costs of treatment.

Supplements

Inclusion and exclusion criteria

Inclusion criteria

1. Age >18 years
2. AChR positive myasthenia gravis (ocular or generalized)
3. Current use of pyridostigmine
4. MGFA Clinical Classification I-IV
5. Receiving a stable dose of MG treatment (other than pyridostigmine). If applicable:
   a. A stable steroid regimen for 1 month
   b. Nonsteroidal immunosuppressants:
      i. Azathioprine, mycophenolate mofetil, cyclosporine or other nonsteroid immunosuppressive agents start > 3 months ago and a stable regimen for 1 month.
      ii. Rituximab start > 6 months ago, complement inhibitors and Fc receptor inhibitors start > 6 months ago and a stable regimen for 3 months.

Exclusion criteria

1. Use of intravenous immunoglobulin or plasma exchange <4 weeks or planned during the trial.
2. Thymectomy < 6 months, or thymectomy (expected) to take place during the trial
3. Use of other AChE inhibitors than pyridostigmine
4. Pregnancy, lactation or intention to become pregnant during the study
5. The patient is unable to fill out the study questionnaires or be interviewed in Dutch, or is unable to undergo the tests needed for the study, or is unable to give informed consent for participation in the study.
6. The investigator can exclude patients for this trial which are deemed not suitable for any reason.

Full list of pyridostigmine side effects queried

Abdominal cramps, stomach ache, nausea, vomiting, diarrhea, flatulence, heartburn, excessive belching, urinary urgency, headache, increased salivation, increased lacrimation, hyperhidrosis, blurred vision, increased bronchial secretion, irregular heartbeat, slow heartbeat, chest pain, light-headedness, fainting, fatigue, blushing, hot flashes, flu-like symptoms (chills, runny nose, coughing up phlegm), tremor, muscle cramps, muscle weakness, muscle twitching, skin rash and hives.

Supplementary Table 4.1 Healthcare costs in the year before inclusion, averaged for those with the costs (n) and averaged over all patients (N)

Unit	n/N	Average costs (€) per patient (n)	Average costs (€) per patient (N)
General practitioner	16/19	88	74
Practice nurse	16/19	32	27
Social worker	19/19	159	159
Physiotherapist	19/19	351	351
Occupational Therapist	19/19	45	45
Speech Therapist	19/19	4	4
Dietitian	19/19	22	22
Psychologist/Psychiatrist	19/19	170	170
Occupational Health Physician	19/19	18	18
Home care			
Household help	3/19	12708	2007
Personal care	1/19	9995	526
Nursing	0/19	0	0
Informal caregiving			
Household help	3/19	1427	225
Personal care	0/19	0	0
Practical assistance	5/19	6918	1821
Emergency department visits	19/19	49	49
Ambulance	0/19	0	0
Outpatient clinic	11/19	796	461
Day treatment	4/19	884	186
Rehabilitation centre	4/19	6191	1303
Hospital admission	1/19	3532	186
Total costs		43389	7634

Supplementary Table 4.2 Non-healthcare in the year before inclusion, averaged for those with the costs (n) and averaged over all patients (N)

Unit	n/N	Average costs (€) per patient (n)	Average costs (€) per patient (N)
Absenteeism	2/19	4779	503
Presenteeism	4/19	4327	911
Productivity losses in the context of unpaid work	7/19	11797	4346
Total costs		**20903**	**5760**

Supplementary Table 4.3 Treatment by period interaction for primary and secondary outcome measures

	Estimate (95% CI)	P-value
Primary outcome		
MGII total	-13.4 (-41.6, 14.7)	0.328
Secondary outcomes		
MGII ocular	-6.2 (-18.3, 5.9)	0.297
MGII generalized	-7.3 (-31.2, 16.7)	0.531
QMG	-0.2 (-11.3, 11)	0.975
MG-ADL	-3.7 (-10.3, 2.9)	0.256
MG-QoL15r	-5.4 (-17.1, 6.2)	0.341
TSQM-9	4.1 (-5.4, 13.7)	0.383

CI, confidence interval; MGII, Myasthenia Gravis Impairment Index; QMG, Quantitative Myasthenia Gravis; MG-ADL, Myasthenia Gravis-Activities of Daily Living; MG-QoL15r, revised 15-item Myasthenia Gravis Quality of Life; TSQM-9, 9-item Treatment Satisfaction Questionnaire for Medication

Supplementary Table 4.4 Laboratory results

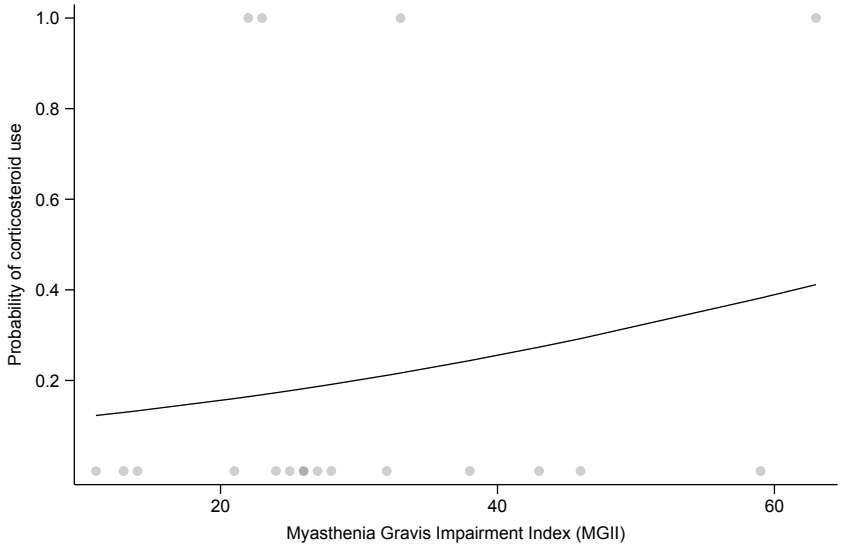
	Baseline N = 19	**Visit 3 N = 19**
Hemoglobin	8.8 (8.3, 9.6)	8.6 (8.2, 9.2)
Unknown	1	0
Hematocrite	0.4 (0.4, 0.5)	0.4 (0.4, 0.4)
Unknown	1	0
Leukocytes	6.6 (5.7, 9.6)	6.6 (5.6, 8.0)
Unknown	1	0
Thrombocytes	244.5 (211.0, 301.8)	243.0 (205.0, 297.5)
Unknown	1	0
Sodium	141.0 (140.0, 143.5)	140.0 (138.0, 142.0)
Potassium	4.6 (4.5, 4.9)	4.3 (4.2, 4.6)
Creatinine	61.0 (56.0, 78.0)	64.0 (55.0, 76.0)
eGFR	90.0 (90.0, 90.0)	90.0 (89.0, 90.0)
Aspartate aminotransferase (ASAT)	22.0 (19.5, 27.0)	21.0 (18.0, 25.0)
Alanine aminotransferase (ALAT)	24.0 (15.5, 26.5)	21.0 (16.5, 30.5)
Alkaline phosphatase	70.0 (63.5, 81.5)	73.0 (61.0, 80.0)
Gamma glutamyltransferase	13.0 (11.0, 23.5)	13.0 (11.0, 22.0)
Creatinine kinase	80.0 (60.5, 103.5)	76.0 (73.0, 122.5)
Glucose	5.0 (4.9, 5.9)	5.4 (5.0, 5.9)
AChR antibodies	9.3 (3.0, 15.7)	10.2 (3.0, 16.2)

Data are median [Q1-Q3]

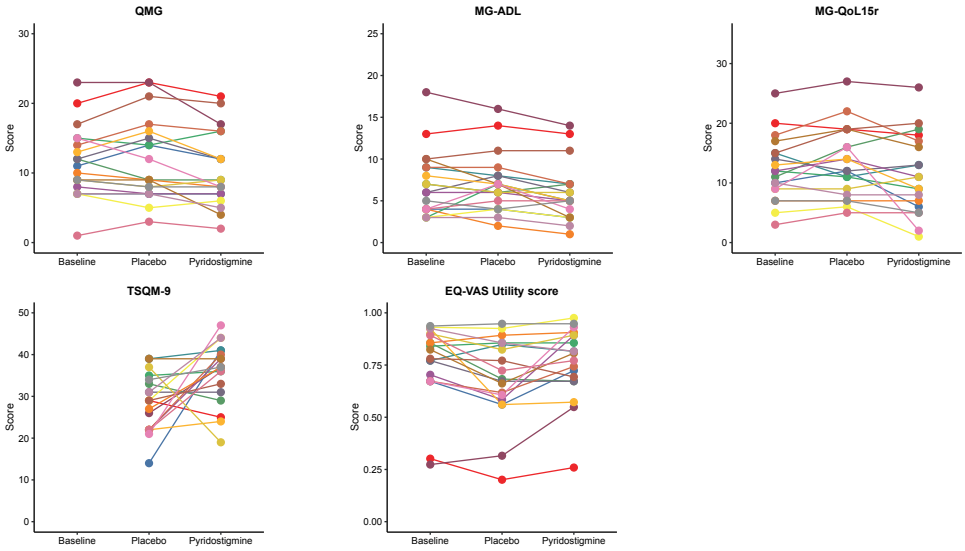
Supplementary Table 4.5 Serum pyridostigmine concentrations

	Baseline N = 19	**Placebo N = 19**	**Pyridostigmine N = 19**
Pyridostigmine concentrations	0.0 (0.0, 1.4)	0.0 (0.0, 0.0)	28.6 (17.9, 40.4)
Unknown	0	1	1

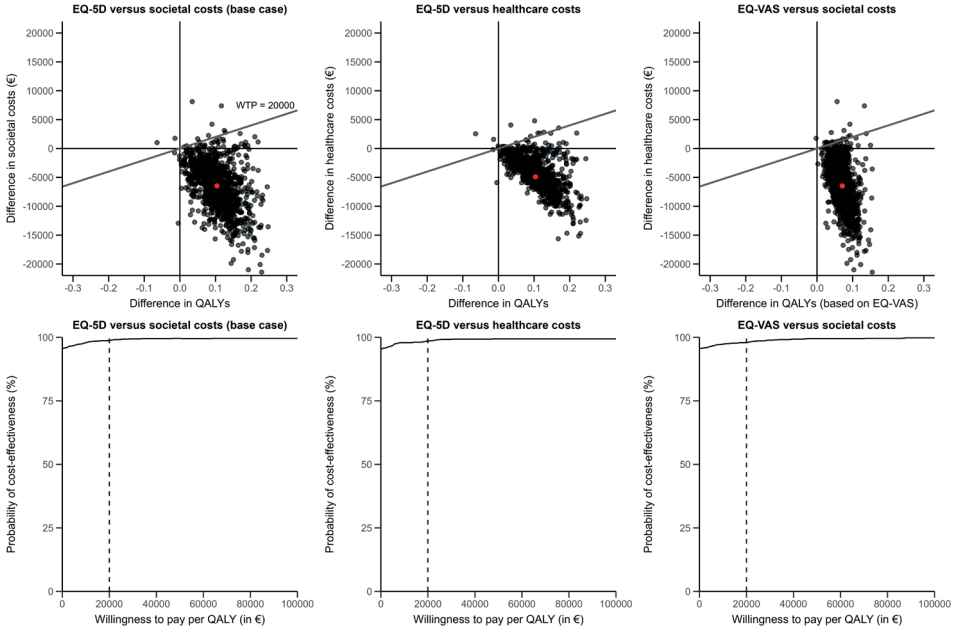
Data are median [Q1-Q3]



Supplementary Figure 4.1 Interaction between corticosteroid use and Myasthenia Gravis Impairment Index at baseline (MGII)
Derived from binary logistic regression analysis.



Supplementary Figure 4.2 Absolute values for each participant at baseline and during treatment with pyridostigmine and placebo for additional secondary outcome measures
QMG, Quantitative Myasthenia Gravis; MG-ADL, Myasthenia Gravis-Activities of Daily Living; MG-QoL15r, revised 15-item Myasthenia Gravis Quality of Life; TSQM-9, 9-item Treatment Satisfaction Questionnaire for Medication; EQ-VAS, EuroQoL-visual analogue scale



Supplementary Figure 4.3 Sensitivity analysis of cost-effectiveness analysis
Top row: cost-effectiveness plane of difference in (a) QALYs derived from EQ-5D versus societal costs (base case) b) QALYs derived from EQ-5D versus healthcare costs, and (c) QALYs derived from EQ-VAS versus societal costs. Bottom row: cost-effectiveness acceptability curves for a) QALYs derived from EQ-5D versus societal costs (base case), (b) QALYs derived from EQ-5D versus healthcare costs, and (c) QALYs derived from EQ-VAS versus societal costs.
QALYs, quality-adjusted life years; EQ-5D, EuroQoL-5 dimensions; EQ-VAS, EuroQoL-visual analogue scale