SYNOPSIS (PROTOCOL WX17798)

COMPANY: Aspreva Pharmaceuticals Corporation NAME OF FINISHED PRODUCT: CellCept® NAME OF ACTIVE SUBSTANCE(S): Mycophenolate mofetil	

TITLE OF THE STUDY	A prospective, randomized, double-blind, placebo-controlled, parallel group, multicenter, 36-week trial to assess the efficacy and safety of adjunct mycophenolate mofetil (MMF) to maintain or improve symptom control with reduced corticosteroids in subjects with myasthenia gravis.		
INVESTIGATORS / CENTERS AND COUNTRIES	A total of 43 centers in 14 countries in North America, South America, Europe, and Asia participated in the study.		
PERIOD OF TRIAL	August 24, 2004 to August 15, 2006	CLINICAL PHASE	3
OBJECTIVES	Primary: to assess the efficacy of MMF therapy compared to placebo in myasthenia gravis (MG) patients receiving prednisone. Secondary: to assess the safety and tolerability of MMF therapy compared to placebo in MG patients receiving prednisone.		
STUDY DESIGN	Prospective, randomized, double-blind, placebo-controlled, parallel group, international multicenter, 36-week, two-arm comparison study of MMF and placebo given as adjunct therapy to underlying treatment with oral prednisone (wherever prednisone was specified, an equivalent dose of other types of oral corticosteroids was allowed).		
NUMBER OF PATIENTS	Planned: 136, with 68 in each treatment group. Enrolled: 176, with 88 in the MMF treatment group and 88 in the placebo group.		
DIAGNOSIS AND MAIN CRITERIA FOR INCLUSION	Male or female patients, 18–80 years old, with diagnosis of MG, and a history of myasthenic weakness involving more than ocular or peri-ocular muscles, positive edrophonium chloride test or abnormal neuromuscular transmission demonstrated by electrodiagnostic testing, and elevated acetylcholine receptor (AChR) antibodies. Patients also were required to have a disease severity history classified by Myasthenia Gravis Foundation of America (MGFA) as II, III, IVa or IVb (a history of classification IVb was allowed, but could not be classified as IVb at study screening and randomization, and could not have severe weakness of oropharyngeal or respiratory muscles, compromised airway protection, MG crisis or impending crisis at study screening and randomization.)		

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DIAGNOSIS AND MAIN CRITERIA FOR INCLUSION (Cont.)	Patients were excluded if they had known hypersensitivity to MMF, were unable to comply with the protocol, were classified as MGFA Class I or V, had a thymoma, or underwent a thymectomy within 6 months prior to randomization.
TRIAL DRUG / STROKE (BATCH) No.	MMF (CellCept®) 500 mg tablets / Lot No. 0222/03
DOSE / ROUTE / REGIMEN / DURATION	MMF 1 g / oral / 2 tablets twice daily (BID) / 36 weeks. Prednisone ≥20 mg/day for at least 4 weeks prior to randomization; dose tapered every 4 weeks to a minimum of 7.5 mg/day according to the protocol-specified taper.
REFERENCE DRUG / STROKE (BATCH) No.	Placebo tablets / Lot No. M0001 and M0002
DOSE / ROUTE / REGIMEN / DURATION	Placebo (0 g) / oral / 2 tablets BID / 36 weeks. Prednisone ≥20 mg/day for at least 4 weeks prior to randomization; dose tapered every 4 weeks to a minimum of 7.5 mg/day according to the protocol-specified taper.
CRITERIA FOR EVALUATION EFFICACY:	Primary parameter: The proportion of patients who reached responder status, as defined by the following criteria: 1. Minimal manifestations or pharmacologic remission (MGFA postintervention status definitions modified) from Week 32 until study termination at Week 36, and 2. Prednisone dose of not more than 7.5 mg/day from Week 32 until study termination at Week 36, and 3. Cholinesterase inhibitor dose of ≤120 mg/day from Week 33 until study termination at Week 36. Patients had one week to reduce the cholinesterase inhibitor dose after reaching 7.5 mg/day prednisone. Secondary parameters were as follows: • Time to start of response, defined as the time that the patient first demonstrated all of the following conditions provided that these conditions were maintained through to study termination at Week 36: 1. Minimal Manifestations or Pharmacologic Remission (MGFA postintervention status definitions modified), and 2. Prednisone dose of 7.5 mg/day, and 3. Cholinesterase inhibitor dose of ≤120 mg/day. • Prednisone dose area under the curve (AUC) • Prednisone dose at study termination • Cholinesterase inhibitor dose at study termination

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EFFICACY: (Cont.)	• Number of intravenous immunoglobulin (IVIG) and plasma exchange (PE) treatments received during the study • Quantitative Myasthenia Gravis Score (QMGS) (change from baseline) • Quality of life measures (36-item short form (SF-36) health survey and Myasthenia Gravis Activities of Daily Living (MG ADL) scale) (change from baseline) • Patient and investigator global assessments (change from baseline) • AChR antibody titers Other parameters were: • Health care utilization questionnaire Sparse sampling population pharmacokinetics (plasma concentration of mycophenolic acid (MPA) and mycophenolic acid glucuronide (MPAG) at Weeks 4, 16 and 28)
SAFETY:	Clinical laboratory tests (hematology, serum chemistry, urinalysis), adverse events (AEs), serious adverse events (SAEs), physical examinations, vital signs (blood pressure and heart rate), electrocardiograms (ECGs), prior and concomitant medications.
STATISTICAL METHODS	Formal hypothesis testing was conducted on the primary efficacy parameter. Fisher's exact test was used to compare response rates between the treatment groups in the intent-to-treat (ITT) population. The primary analysis was tested with a two-tailed test (alpha=0.05). A logistic regression analysis was performed to adjust for factors potentially prognostic of outcome (age of onset of MG, duration of disease, gender, prior thymectomy, and the interactions of treatment with these factors). A Cochran-Mantel-Haenszel procedure was conducted to compare response rates in treatment groups stratifying by pooled center. For secondary efficacy endpoints, support was provided by the 95% confidence interval, when applicable. For all secondary efficacy outcomes assessed by visit, descriptive analyses were carried out by visit and early termination in the ITT population using observed cases (no imputation performed for missing assessments). In addition, the endpoint was also summarized, where applicable, and was defined using the assessment at early termination or Week 36. If a patient was not evaluated at early termination, then imputation for endpoint was performed using last observation carried forward (LOCF). Concentrations of MPA and MPAG were analyzed and presented descriptively.

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METHODOLOGY:

After screening and determination of eligibility, patients with MG were randomized to receive either MMF 1 g BID or matching placebo orally for 36 weeks. Patients were required to receive prednisone (or equivalent dose of other corticosteroid) at a dose of ≥20 mg/day (or equivalent alternate day dose) for at least 4 weeks prior to randomization and at baseline, with dose reduction to a minimum of 7.5 mg/day. After baseline assessments and randomization, patients returned at Weeks 2, 4, 8, 12, 16, 20, 24, 28, 32, and 36 for assessments of efficacy, safety, and prednisone and cholinesterase inhibitor dose reductions according to the guidelines.

Of the 233 patients screened, 176 patients were randomized to the two treatment groups: 88 patients to each group (MMF and placebo). The proportion of patients who completed the 36 weeks of treatment was similar (80.7% placebo group, 83.0% MMF group). The ITT and Safety populations consisted of all patients who were randomized and received at least one dose of study medication (88 in each group). The per-protocol (PP) population (166 patients: 79 placebo and 87 MMF) included patients who completed the study, were treated as randomized, and had no major protocol violations. More patients in the placebo group (9/88, 10.2%) than in the MMF group (1/88, 1.1%) were excluded from the PP population.

The demographics of the two treatment groups were similar: 45.5% were male in the placebo group and 47.7% were male in the MMF group; the mean age was 49.7 years in the placebo group and 49.0 years in the MMF group; and most patients were Caucasian (77.3% of the overall population). Baseline disease characteristics were also similar between the two groups.

EFFICACY RESULTS:

For the primary efficacy parameter of response, there was no difference between the treatment groups. In the ITT population, 38.6% of the placebo patients and 44.3% of the MMF patients met the criteria for response (p=0.541). When the primary efficacy parameter was adjusted for factors potentially prognostic of outcome, there was no difference between the groups for response.

For each of the secondary efficacy endpoints of time to start of response, cholinesterase inhibitor dose, QMGS, quality of life, and investigator and patient global assessments, the results between the two treatment groups were similar and consistent with the results of the primary endpoint. For the secondary endpoint of prednisone dose, although there appeared to be no meaningful difference between the MMF and placebo groups, substantially fewer patients in the MMF group (n=1) were unable to reduce their prednisone dose and were prematurely terminated from the study compared to the placebo group (n=8). For the secondary efficacy endpoints regarding the number of IVIG and PE treatments and AChR antibody titers, the results suggested differences between the two treatment groups. Fewer patients in the MMF group (n=3) received an IVIG and/or PE treatment compared to the placebo group (n=8), suggesting that MMF use may reduce the need for administration of these rescue medications. In addition, MMF patients showed a larger decline in AChR antibody titers (with median values of 8.00 nmol/L at Week 0 and 3.46 nmol/L at Week 36) compared to patients in the placebo group (with median values of 8.00 nmol/L at Week 0 and 7.61 nmol/L at Week 36); this difference suggests MMF may play a role in decreasing circulating AChR antibody levels over the course of 36 weeks.

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PHARMACOKINETIC RESULTS:

In the MMF treatment group, mean MPA levels ranged from 4.61 to 5.20 µg/mL, and mean MPAG levels ranged from 61.4 to 63.1 µg/mL. These concentrations were reflective of levels expected in patients who were taking MMF 1 g BID. The levels seen in the placebo group (0.10 µg/mL for MPA and 4.00 µg/mL for MPAG) reflect the lower limit of quantification.

SAFETY RESULTS:

Extent of exposure to study medication was similar between the treatment groups. A similar proportion of patients received study medication through Week 36 and the mean duration of treatment was 236.0 days in the placebo group and 229.7 days in the MMF group.

The overall incidence of AEs was similar between the treatment groups (84.1% placebo vs 80.7% MMF); however, the incidence of SAEs was greater in the MMF group compared to the placebo group (15.9% placebo vs 21.6% MMF).

AEs most commonly occurred in the system organ classes were infections and infestations (39.8% in the placebo group and 44.3% in the MMF group), musculoskeletal disorders (28.4% in each group), gastrointestinal disorders (30.7% in the placebo group and 22.7% in the MMF group), and nervous system disorders (21.6% in each group). For individual events, headache (12.5%), myasthenia gravis (11.4%), and nausea (9.1%) were the most frequent in the MMF group. Myasthenia gravis (20.5%), diarrhea (10.2%), and muscle spasms (10.2%) were the most common events reported in the placebo group.

Overall, the proportion of patients who experienced a severe AE was similar in the two groups (18.2% in the placebo group and 17.0% in the MMF group). The proportion of patients who experienced an AE considered related to study drug was higher in the placebo group (45.5% compared to 37.5% in the MMF group).

Three patients died; two of the deaths occurred while on study and one occurred 11 days after the patient completed the study. One patient in the MMF group died due to pneumonia, considered by the investigator to be possibly related to treatment. The other two deaths (alcohol poisoning in a patient in the placebo group and hemorrhagic fever in a patient in the MMF group) were considered unrelated to treatment.

A total of 46 SAEs occurred in 33 patients in both treatment groups, with the highest incidence in the MMF group (15.9% of placebo patients and 21.6% of MMF patients experienced at least one SAE). A similar proportion of patients withdrew from treatment due to AEs in each group (4 placebo patients and 3 MMF patients).

CONCLUSIONS:

Results of this Phase 3 study showed that 44.3% of patients who received MMF together with a background therapy of oral corticosteroids and cholinesterase inhibitors demonstrated good disease control with steroid sparing; this was similar to the 38.6% of patients who received only background therapy and demonstrated good disease control with steroid sparing. The results indicated no difference between treatment groups with respect to the primary efficacy response in MG patients.

The addition of MMF to background therapy was generally well tolerated; the frequency, nature, and severity of AEs were generally similar between the two treatment groups.