SYNOPSIS (PROTOCOL WX18411)

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

TITLE OF THE STUDY	An optional continuation of double-blind treatment for patients who have achieved good symptom control with stable prednisone dosing and who have completed Protocol WX17798 (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 patients with myasthenia gravis).
INVESTIGATORS / CENTERS AND COUNTRIES	This study was conducted by 17 investigators from 17 centers in 8 countries.

PERIOD OF TRIAL	January 6, 2005 to November 1, 2006	CLINICAL PHASE	3

OBJECTIVES	To address investigator concerns about post-study treatment of patients who did well on double-blind treatment in Protocol WX17798 by providing the option to continue double-blind treatment until treatment assignment could be unblinded following database lock.
STUDY DESIGN	Continuation of double-blind treatment according to treatment assignment for Protocol WX17798. Visit 12 of Protocol WX17798 coincided with Visit 1 of this study. Patients returned at 8 week intervals for all safety assessments, except hematology, until withdrawal or database lock. Hematology safety assessments were initially conducted at 4 week intervals until Week 16 and every 8 weeks thereafter. During this continuation study, the dose of prednisone and cholinesterase inhibitors could be adjusted as clinically indicated.
NUMBER OF PATIENTS	There were 38 randomized patients; 14 randomized to placebo and 24 randomized to MMF.
DIAGNOSIS AND MAIN CRITERIA FOR INCLUSION	Diagnosis of Myasthenia gravis. Completed 36 weeks treatment with double-blind MMF or placebo in Protocol WX17798. Achieved good symptom control with a stable prednisone dose for the final four weeks of that study. Good symptom control was defined as Minimal Manifestations or Pharmacologic Remission (Myasthenia Gravis Foundation of America (MGFA) Postintervention status modified) from Week 32 until study termination at Week 36. Stable prednisone dose was defined as no change in prednisone dose after Week 32.

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TRIAL DRUG / STROKE (BATCH) No.	MMF (CellCept®) 500 mg tablets / Lot Nos. 0222/03; 0222/07; 0222/08.
DOSE / ROUTE / REGIMEN / DURATION	MMF 500 mg / oral / 2 tablets twice daily
REFERENCE DRUG / STROKE (BATCH) No.	Placebo tablets / Lot Nos. M0001; M0002; M0003; M0004.
DOSE / ROUTE / REGIMEN / DURATION	Two placebo tablets orally twice daily (morning and evening).
CRITERIA FOR EVALUATION EFFICACY:	No efficacy outcomes were measured.
SAFETY:	Clinical laboratory tests (hematology, serum chemistry, urinalysis), adverse events (AEs), physical examinations, vital signs (blood pressure (BP) and heart rate), electrocardiograms (ECGs) and concomitant medications.
STATISTICAL METHODS:	All patients taking at least one dose of the trial medication and with a follow-up safety assessment were included in the safety analysis. Values were tabulated with descriptive statistics by treatment group across the course of the study. Abnormal values were listed by treatment group. AEs were coded and tabulated by body system, severity and relationship to study medication. Serious adverse events (SAEs) and AEs leading to premature study withdrawal were summarized separately.

METHODOLOGY:

Double-blind treatment was continued according to treatment assignment from Protocol WX17798, until the database for WX17798 was locked and unblinded. Duration of individual treatment depended on the interval between completion of Protocol WX17798 and the unblinding of the treatment assignments.

EFFICACY RESULTS:

No efficacy outcomes were measured.

PHARMACODYNAMIC RESULTS:

No pharmacodynamic outcomes were measured.

PHARMACOKINETIC RESULTS:

No pharmacokinetic outcomes were measured.

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SAFETY RESULTS:

All 38 patients in the study were eligible for the safety analysis. The mean treatment duration in the placebo group was 391.07 ± 70.55 days, compared with 407.58 ± 105.740 days in the MMF group. However, individual treatment duration varied and some patients participated in this continuation study for a very short period. MMF was generally well tolerated in this small study population of 24 MMF patients and 14 placebo patients. No patients died in this study. The overall incidence of AEs was higher in the placebo group (57.1%, 8 patients) compared with the MMF group (45.8%, 11 patients). Generally, the increased incidence of infections and diarrhea in the MMF group was the most noticeable difference between the two treatment groups and this is consistent with the established safety profile of MMF. The MMF group also received higher corticosteroid doses during Study WX18411 compared with the placebo group. Patients in the MMF group who experienced infections also had a higher incidence of pre-existing medical conditions associated with an increased risk of infection. Of the infections reported in the MMF group, the incidence of treatment related infections was low (8.3%, 2 patients). Similarly in the MMF group, the incidence of severe infections reported as AEs was low (12.5%, 3 patients), and the incidence of infections reported as SAEs was low (8.3%, 2 patients). Both of these infections reported as SAEs in the MMF group had resolved by the final visit. No MMF patients withdrew from treatment as a result of an AE of infection.

The incidence of laboratory abnormalities was low in both treatment groups. No noticeable trends were seen for laboratory abnormalities in either treatment group and in particular lymphopenia and leukopenia, which are known adverse effects of MMF from the published literature. No clinically significant differences were observed between the treatment groups for physical examinations, blood pressure, heart rate and ECG assessments.

It is difficult to draw any conclusions regarding the comparative safety data for the core and continuation studies, for a number of reasons. The small number of patients entering the continuation study from the core study, the variation in treatment duration in the continuation study, and the entry of patients into the continuation study on the basis of their post-randomization safety experiences, amongst other factors, biases any inferences that could be made about long-term safety.

Overall however, the safety profile of MMF in the Continuation Study WX18411 is broadly consistent with the Core Study WX17798 data, and the published data on MMF. In particular, the rate of infections and diarrhea seen in this study appear to be consistent with the published data. The addition of MMF to concomitant corticosteroid and anticholinesterase therapy did not result in any new safety concerns.

CONCLUSIONS:

MMF treatment was generally well tolerated in this small long-term safety study with exposure to MMF up to 92 weeks. AEs that occurred with MMF treatment in this study were consistent with the safety profile of MMF.