SYNOPSIS (PROTOCOL WX17796)

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

TITLE OF THE STUDY	A prospective, randomized, double-blind, placebo-controlled, parallel group, multicenter, 52-week trial to assess the efficacy and safety of adjunct MMF to achieve remission with reduced corticosteroids in subjects with active pemphigus vulgaris.		
INVESTIGATORS / CENTERS AND COUNTRIES	A total of 21 centers in 8 countries (Canada, Germany, India, Israel, Turkey, Ukraine, the United Kingdom, and the United States) participated in the study.		
PERIOD OF TRIAL	May 11, 2004 to October 17, 2008	CLINICAL PHASE	3
OBJECTIVES	Primary: To assess the efficacy (disease control with steroid-sparing) of MMF therapy compared to placebo in patients with pemphigus vulgaris (PV) receiving prednisone. Secondary: To assess the safety and tolerability of MMF therapy compared to placebo in PV patients receiving prednisone during the study treatment period (52 weeks); and to assess the safety experience of PV patients following active randomized treatment with MMF (or placebo) in combination with a regimen of steroid tapering.		
STUDY DESIGN	Prospective, randomized, double-blind, placebo-controlled, parallel group, international multicenter, 52-week, study of MMF (2 g/day or 3 g/day) or matching placebo given in combination with oral prednisone (wherever prednisone was specified, an equivalent dose of other types of oral corticosteroids was allowed).		
NUMBER OF SUBJECTS	Planned: 92 subjects Actual: 96 subjects		

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DIAGNOSIS AND MAIN CRITERIA FOR INCLUSION	Male or female subjects, 18–70 years old, with diagnosis of mild or moderate PV within the past 24 months, showing histological features of acantholysis, and tissue-bound immunoglobulin G (IgG) antibodies as observed by direct immunofluorescence on the surface of affected epithelium, or circulating IgG antiepithelial antibodies binding the epithelial cell surfaces by indirect immunofluorescence; and in the judgment of the investigator would benefit from a short-term oral prednisone dose at baseline of 1-2 mg/kg/day. Subjects were excluded if they had known hypersensitivity to MMF, were unable to comply with the protocol, had evidence of paraneoplastic pemphigus or other autoimmune blistering disease other than PV; had major physical or psychiatric illness or major traumatic injury 6 month prior to randomization; had clinically significant active medical condition, other autoimmune disease or other medical condition, which in the investigator's opinion was associated with increased risk to the subject or would interfere with study assessments and outcomes.
TRIAL DRUG / STROKE (BATCH) No.	MMF 500 mg tablets / Lot Nos. 0222/03, 0222/07, and 0222/09
DOSE / ROUTE / REGIMEN / DURATION	MMF 2 g / oral / 4 tablets twice daily (BID) / 52 weeks MMF 3 g / oral / 6 tablets BID / 52 weeks
REFERENCE DRUG / STROKE (BATCH) No.	Placebo tablets / Lot Nos. M0001, M0002, M0003, and M0006
DOSE / ROUTE / REGIMEN / DURATION	Placebo / oral / 4 tablets BID / 52 weeks Placebo / oral / 6 tablets BID / 52 weeks

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CRITERIA FOR EVALUATION	
EFFICACY:	Primary parameter: The proportion of subjects achieving responder status (no new persistent lesions at Week 52 and a prednisone dose ≤10 mg/day during Weeks 48–52) in the two active treatment groups combined (2 g/day and 3 g/day MMF) versus the placebo group. Key secondary parameters: 1. Time to relapse for subjects who previously had a response 2. Time to initial response 3. Number of days a subject maintained a prednisone dose of not more than 10 mg/day in the absence of new persistent lesions Secondary parameters were as follows: • Proportion of responders in 2 g/day MMF, 3 g/day MMF and placebo • Prednisone dose • Prednisone cumulative dose • Lesion counts and assessment • Quality of life (36-item short form health survey) • Subject and investigator global assessments (change from baseline) • Desmoglein-1 and desmoglein-3 antibody titers Other parameters were: • Health care utilization questionnaire • Sparse sampling population pharmacokinetics (plasma concentration of mycophenolic acid (MPA) and mycophenolic acid glucuronide (MPAG))
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, prior and concomitant medications.

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STATISTICAL METHODS	For the primary endpoint, response rates between the placebo group and the MMF group (both dose groups combined) were compared using a Fisher's exact test (primary analysis) and 97.5% exact confidence interval (CI) (supportive analysis). Subjects not achieving responder status were considered non-responders. The consistency of a trend between the response to 2 g/day MMF treatment and the response to 3 g/day MMF treatment relative to placebo was assessed using descriptive methods (ie, difference in response rates between each of the MMF dose groups and the placebo group and 95% exact CIs). A formal trend test was not performed. If primary efficacy was established, the key secondary endpoints were tested in a hierarchical manner; testing would stop when a result was not significant at the 0.025 level. All statistical tests were two-sided. The key endpoints were tested in the following order: (1) time to relapse, (2) time to initial response, and (3) prednisone dose maintenance. Inferential testing was not performed for the other secondary endpoints. Each of the active treatment arms (2 g/day and 3 g/day MMF) were separately compared to placebo for the proportion of subjects with response, as defined for the primary endpoint. All other secondary efficacy analysis was conducted for the combined MMF treatment groups (2 g/day and 3 g/day MMF combined) versus the placebo group.

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METHODOLOGY:

After screening and determination of eligibility, subjects were randomized to receive either MMF (2 g/day or 3 g/day) or matching placebo orally for 52 weeks. Subjects also received oral prednisone, with a dose at randomization (baseline) of 1–2 mg/kg/day (based on ideal body weight and to the nearest multiple of 10 mg) or equivalent alternate-day dose, with dose tapering to achieve a target of 10 mg/day. After baseline assessments and randomization, subjects returned at Weeks 2 and 4, and every 4 weeks thereafter until Week 52 for assessments of efficacy, safety, and prednisone dose reductions according to protocol-specified guidelines.

A total of 96 subjects were randomized: 37 to placebo, 22 to MMF 2 g/day, and 37 to MMF 3 g/day. Two subjects (1 placebo and 1 in the MMF 2 g/day group) did not receive study drug because they were mistakenly randomized. Of the 94 dose subjects, the proportion that completed treatment was similar across the treatment groups: 80.6% placebo, 85.7% MMF 2 g/day, and 75.7% MMF 3 g/day. The intention-to-treat, per-protocol and safety populations consisted of all 94 dosed subjects. There were no major protocol violations.

Overall, subjects were similar across dose groups with respect to age; the mean ± standard deviation age was 44.3 ± 13.48 years (with a range of 17–73 years). In general there were more women than men; both the placebo and MMF 2 g/day groups had 2-times more women than men (67% women versus 33% men), whereas, the MMF 3 g/day group had a similar proportion of women and men (49% versus 51%, respectively). While most subjects were either White or Asian (overall 57% versus 38%, respectively), there were notably more Asians (67%) in the MMF 2 g/day group compared to the placebo group (39%) or the MMF 3 g/day group (22%). There was also an apparent difference with respect to weight; subjects in the MMF 2 g/day group were lighter than placebo or MMF 3 g/day cohorts (with mean weights of 41 kg versus 46 kg versus 45 kg, respectively).

EFFICACY RESULTS:

On a background of prednisone, the proportion of subjects treated with MMF who had no new or persistent lesions at Week 52 and had successfully tapered their prednisone dose to ≤10 mg/day during Weeks 48–52 was similar to that for subjects treated with placebo (69.0% MMF, 63.9% placebo; difference (MMF−placebo) 5.1%; 97.5% CI: −17.4, 27.6; p=0.6558).

Of the subjects who had at least an initial response, those treated with MMF showed longer times to relapse compared to placebo subjects although the comparison failed to achieve statistical significance.

Although not statistically significant, MMF-treated subjects had an initial response to treatment, satisfying both responder criteria, approximately 6 weeks sooner than placebo subjects. In addition, MMF subjects had a quicker time to sustained response, approximately 14 weeks sooner than placebo subjects.

MMF-treated subjects were at a lower maintenance dose of prednisone for a longer period of time than placebo subjects; and the overall median total prednisone dose for MMF subjects was approximately 1000 mg less than that for subjects in the placebo group. Although these comparisons between MMF- and placebo-treated subjects were not statistically significant, they are clinically important.

There was no meaningful difference in quality of life measures between subject groups.

MMF subjects were more likely to indicate marked improvement in their disease status compared to placebo subjects; this result was also observed with the investigator's global disease assessment.

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PHARMACOKINETIC RESULTS:

The pharmacokinetics (PK) of MPA were well described by a 2-compartment open model with first order absorption following a short lag time and first order elimination from the central compartment. Body weight and albumin were found to contribute to inter-individual variance in clearance. The pharmacokinetics of MPAG were well described by a 1-compartment open model with a formation rate equivalent to the fraction of MPA cleared from the central compartment as MPAG with first order elimination from the central compartment of the metabolite. There was no effect of covariates on MPAG clearance.

SAFETY RESULTS:

The majority of AEs were mild or moderate and most frequently involved infections and infestations (which appeared to be treatment (MMF) and dose-dependent) and skin and subcutaneous tissue disorders. Pemphigus was the most frequently reported AE, with a similar incidence (30–33%) across treatment groups. In the MMF 3 g/day treatment group frequently reported AEs included oral candidiasis, headache, and upper respiratory tract infection, which occurred with a higher frequency than in the placebo or MMF 2 g/day groups. The MMF 2 g/day group had the highest incidence of nasopharyngitis, pyrexia, cough, hypertension and arthralgia.

During the treatment period, 8 subjects (4 placebo subjects, 4 MMF subjects) experienced at least one SAE (10 SAEs in total), which included 1 death (cardiovascular insufficiency in a placebo subject). During the follow-up period, 1 subject (who had received MMF 3 g/day during the treatment phase and no MMF during the follow-up period) became pregnant approximately 6 weeks after MMF treatment had ended and had a miscarriage approximately 6–7 weeks following the estimated conception.

While laboratory values generally remained normal over the course of the study, one subject in the MMF 3 g/day group experienced severe lymphopenia and severe neutropenia and was subsequently withdrawn from the study.

CONCLUSIONS:

Although the primary objective did not show a difference between MMF and placebo treatments, MMF demonstrated clinical utility, with substantial short- and long-term benefits to subjects with PV. Based on the secondary objectives of the study, although not statistically significant, MMF treatment produced a quicker time to response, a quicker time to sustained response, a longer sustained response, a longer time in remission, and a longer time to relapse compared to placebo. MMF-treated subjects also had substantially lower total exposure to corticosteroids over the 52-week study compared to placebo-treated subjects, which has clinically meaningful benefits. In addition, MMF was well tolerated over the long-term in this patient population.