SYNOPSIS

Name of Sponsor/Company: Astellas Pharma China, Inc.	
Name of Finished Product: Tacrolimus Capsules	
Name of Active Ingredient: Tacrolimus	
Title of Study:A Randomized, Double-Blind, Placebo-Control, Multicenter Clinical Trial evaluating the Efficacy and Safety of Tacrolimus Capsules in the Treatment of Myasthenia Gravis Patients with Inadequate Response to Glucocorticoid Therapy	
Investigators: Prof [redacted] and Prof [redacted].	
Publication(s) [reference(s)]:Appendix 14	
Study Period: Initiation Date:30 March 2011	**Last Evaluation:**22 May 2014
Objective: The objective of this trial was to evaluate the efficacy and safety of tacrolimus capsules in the treatment of myasthenia gravis(MG) patients with inadequate response to glucocorticoid therapy.	
Methodology: The trial was a randomized, double-blind, placebo-control, multicenter clinical trial evaluating the efficacy and safety of tacrolimus capsules in the treatment of Chinese MG patients with inadequate response to glucocorticoid therapy.	
Number of Subjects (planned and analyzed): Number of subjects planned: 80 Number of subjects analyzed: 83	
Diagnosis and Main Criteria for Inclusion: Male or female Chinese patients aged between 18 and 70 with a definite diagnosis of MG, a quantitative myasthenia gravis (QMG) score ≥7 and an inadequate response to glucocorticoid therapy.	

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Test Product, Dose and Mode of Administration:

Tacrolimus at a single dose level of 3× 1 mg capsules (lot numbers: [redacted] and [redacted]) administered once daily after an evening meal for 24 weeks.

Reference Therapy, Dose and Mode of Administration:

Placebo capsules (lot number: [redacted]) with the same appearanceas the tacrolimus capsules administered as test product.

Criteria for evaluation:

***Efficacy*:**

Primary Efficacy endpoint:

- Improvement of QMG score at the end of the trial.

Secondary efficacy endpoints:

- Improvement of Osserman classification at the end of the trial
- Improvement of MG Activities of Daily Living (ADL) Scale at the end of the trial
- Improvement of manual muscle test (MMT) at the end of the trial
- Retention rate of the drug and drop-out rate due to failure of treatment at the end of the trial (retention rate was defined as number of patients who completed the trial / number of patients receiving drugs at the beginning of the trial ×100%)
- The reduction of the dose of glucocorticoid at the end of the trial

***Safety*:**

Safety variables were:

- Adverse events (AEs);
- Laboratory tests (hematology, biochemistry, urinalysis, and blood lipids);

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- Vital signs (blood pressure, pulse, respiratory rate, and body temperature);
- Height and weight (including body mass index);
- Physical examination;
- Electrocardiogram (ECG) examination;
- Tacrolimuswhole blood concentrations.

Statistical Methods:

Trial Population:

All patients randomized were included in the All Randomized population. All randomized patients who received at least one trial drug were included in the Safety Set (SS). All randomized patients who received at least one trial drug and who had at least one efficacy measurement after the first treatment were to be included in the Full Analysis Set (FAS) according to the principle of intention to treat. The Per-Protocol Set (PPS) was to include all randomized patients who had good compliance (dose administered was 80% to 120% of dose planned), who did not use any prohibited drugs, and who had no efficacy protocol deviations/violations during the trial.

Statistical Methods:

Summary descriptive statistics of categorical data were presented as frequencies and percentages in each category. Summary descriptive statistics of continuous data were presented as number of observations, mean, standard deviation (SD), median, quartile 1, and 3 (Q1 and Q3), minimum, and maximum. For difference test, statistical data and P-values were provided. All significance testing was two-tailed at the 0.05 significance level.

Efficacy analysis was conducted by using both FAS and PPS, in which, FAS dominated and PPS was for reference. The difference between FAS and PPS was discussed in the trial. Safety analysis was conducted using the SS.

The analysis sets were determined in the blind data review meeting (BDRM) attended by the investigator, sponsor, data manager and statistician. The materials used in the BDRM were provided by the data manager and the statistician.

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Demographic and Baseline Characteristics

Demographic and baseline characteristics were listed and summarized by treatment group and overall for FAS, SS, and PPS. Standard descriptive statistics were presented for the continuous variables. For the continuous variables, t-test was used to compare between the two treatment groups and Fisher exact test was used for categorical variables between the two treatment groups.

Medications received prior to or concomitantly with treatment were coded using the World Health Organization Drug Dictionary (B2 DDE March 2013) Anatomical Therapeutic Chemical Classification codes.

PrimaryEfficacy Analysis

Analysis of covariance was used to compare the difference of change of total QMG scores between two groups after treatment for data using last observation carried forward (LOCF) by fitting general linear model (GLM) in FAS. The GLM was fitted for observed cases (OC) as well. The response variable was the difference in QMG score between baseline (Day 0) and at the end of the trial. The independent variables were the baseline QMG score and treatment group.

For the primary efficacy endpoint, the estimate of the mean change in QMG Score between Visit 8 (Week 24) and baseline were reported. For the difference between treatment groups, the estimate of the mean difference of the change in QMG score between Visit 8 (Week 24) and baseline were reported, along with 95% confidence interval (CI) and two-sided P-value.

A mixed-effects model was fitted using observed case (OC) in FAS for supportive analysis. The response variable was the difference in QMG Score between baseline and each post baseline visit. The explanatory variables were baseline QMG score, treatment group, visit, and interaction terms between visit and treatment. All terms were fitted as fixed effects. Supportive analysis was also performed using the PPS, including mixed model and GLM on OC, but LOCF was not used for PPS analysis. Compound symmetry was used to fit the model and an unstructured variance-covariance structure was used for supportive analysis.

Summary of QMG score at each visit and changes from the baseline are provided for OC and cases using LOCF in FAS and for OC only in PPS. P-values for the difference of changes of total scores at each visit between two groups are provided from GLM.

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Secondary EfficacyAnalysis

For the secondary endpoints, MG-ADL Scale, MMT (total, cranial nerves muscle strength, and human body muscle force), and dose of glucocorticoid. The GLM were similar to those used for the primary endpoint analysis to compare the score change or dose change from baseline between two treatment groups. The covariate of baseline was changed based on each secondary endpoint.

All analyses of secondary endpoints were produced using FAS and PPS on OC.

Osserman Classification

Osserman classification at baseline andVisit 8 (Week 24)are summarized by treatment group. Mann-Whitney U test was used to compare the grading change from baseline between the two treatment groups.The two-sided P-value is reported.

Retention Rate of the trial drug and drip-out rate due to failure of treatment

Retention rate of the trialdrug and drop-out rate due to failure of treatment at the end of the trial are summarized and compared using a Fisher's exact test between the two treatment groups.

Safety Analysis

The total number of AEs reported was presented for the SS. In these "event level" analyses, all AEs were counted separately. The number and percentage of patients experiencing AEs were presented for the SS. In these "patient level" analyses, multiple AEs within the same category for a particular patient were only counted once and the denominator for the percentage calculation was the number of patients in the SS. The number and percentage of patients experiencing each AE are tabulated by system organ class andpreferred term inMedical Dictionary for Regulatory Affairs (MedDRA, version 16.1) for the SS.

Laboratory tests, vital signs and body weightwere summarized by visit (including end of treatment) and treatment group using descriptive statistics (number of patients, mean, SD, median, and minimum, and maximum). The same statistics were summarized for change from baseline of each visit.

In addition, shift tables by treatment group were presented for each laboratory test (cross-tabulations of below the lower limit of the normal range, within the limits of the normal range

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or above the upper limit of the normal range at baseline versus scheduled visits).

The number and percentage of patients with physical examination abnormalities were presented by treatment group at screening and last visit for the SS.

The number and percentage of patients with normal or abnormal ECG results were presented by visit and treatment group for the SS. Shifts from baseline (normal to abnormal, abnormal to normal) at last visit were presented on the same table.

Summary/Conclusions:

Efficacy Results:

The primary efficacy endpoint of this trial was improvement of QMG score at the end of the trial. The decrease in QMG score from baseline was larger for the tacrolimus treatment group than for the placebo treatment group at Week 24 but the difference did not reach statistical significance. However, decrease change from baseline QMG mean score was consistently larger for the tacrolimus treatment group than for the placebo treatment group.

Supportive analyses using a compound symmetry and unstructured mixed effects model were used. The LS mean difference in QMG score at Week 24 versus placebo reached statistical significance for both the compound symmetry model and the unstructured covariance structure (-1.9 [p = 0.012] and-1.8 [p = 0.046], respectively).

Decrease change from baseline scores were consistently larger for the tacrolimus treatment group for ADL, MMT, and human body muscle force. In addition, there were consistently more patients whose Osserman grade had decreased from baseline by 1 grade or greater in the tacrolimus treatment group. However, there were no statistically significant differences between the tacrolimus treatment group and the placebo treatment group for the secondary efficacy endpoints at Week 24.

The drug-retention rate was high and the drop-out rate due to treatment failure was low for both treatment groups. There was no statistically significant difference between the treatment groups.

Safety Results:

The safety analysis was performed on 83 patients.

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Overall, 67 (80.7%) patients reported at least 1 AE regardless of severity, 31 (81.6%) patients in the placebo treatment group and 36 (80.0%) patients in the tacrolimus treatment group. Based on the Fisher exact test, there was no statistically significant difference in the number of patients reporting AEs between the two treatment groups (p = 1.000).

The distribution of AEs according to severity was similar across the treatment groups. The majority (63 patients, 75.9%) reported AEs of mild severity with 18 patients (21.7%) reporting AEsAEs of moderate intensity and 6 patients (7.2%) reporting AEs of severe intensity overall. Severe AEs were reported by 3 (6.7%) patients in the tacrolimus treatment group and 3 (7.9%) patients in the placebo treatment group. None of the patients reported an unknown severity.

Drug-related AEs were identified by the investigator as being at least possibly related to the trial drugor the causality is unknown. Overall, 62 patients (74.7%) reported potentially drug-related AEs. The distribution of potentially drug-related AEs was similar across the treatment groups, and presented no statistically significant difference (p = 0.804), 33 patients (73.3%) in the tacrolimus group and 29 patients (76.3%) in the placebo treatment group. The most frequently reported potentially drug-related AEs were upper respiratory tract infection (18.1%), MG (15.7%), nasopharyngitis (13.3%), diarrhoea (10.8%), hypertension (6.0%), bronchitis (4.8%), urinary tract infection (4.8%), and diabetes mellitus (3.6%).

Eleven (13.3%) patients reported SAEs with no statistical difference between the two groups (p = 0.747). Serious AEs included MG (8.4%), bronchitis (2.4%), lung infection (2.4%), atrial fibrillation (1.2%), diabetes mellitus (1.2%), and dyspnoea (1.2%).

Adverse events leading to permanent withdrawal of trial drug were reported by 6 patients (7.2%) and 5 events were assessed as being SAE and related to treatment.

No deaths were reported during this trial.

Increases in blood glucose were observed in the tacrolimus treatment group at Week 4 and Week 12 without a corresponding increase in the placebo group. In addition to this, HBA1c was considered to be high and clinically significant in 9/45 patients in the tacrolimus treatment group compared to 4/38 patients in the placebo treatment group. There was also a consistently larger decrease in change from baseline ALT values in the tacrolimus treatment group compared to the placebo treatment group.

The proportion of patients with elevated blood lipids was lower in the tacrolimus group than

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in the placebo group.

There were no notable trends in vital signs or abnormal ECG findings over time or differences between the treatment groups. In addition there were no notable differences in weight or BMI change from baseline between the treatment groups.

Conclusion(s):

The primary efficacy endpoint of this trial was improvement of QMG score at the end of the trial and although the primary efficacy endpoint did not reach statistical significance, QMG change from baseline score showed a clinically significant decrease in the tacrolimus treatment group. The adjusted mean change from baseline in QMG score at Week 24 was -4.9 for the tacrolimus treatment group and -3.3 for the placebo treatment group with a LS mean difference of -1.7 and a p-value of 0.067.

Tacrolimus3 mg capsules administered once daily for 24 weeks were well tolerated. Overall, 67 (80.7%) patients reported at least 1 AE regardless of severity, 31 (81.6%) patients in the placebo treatment group and 36 (80.0%) patients in the tacrolimus treatment group. The most frequent AEs by preferred term were upper respiratory tract infection (20.5%), nasopharyngitis (19.3%), MG (16.9%), and diarrhoea (14.5%). Based on the Fisher exact test, there was no statistically significant difference in the number of patients reporting AEs between the two treatment groups (p = 1.000). There were no deaths during the trial.

There were more patients with clinically significant elevated blood glucose and glycated haemoglobin in the tacrolimus treatment group than in the placebo groupThe proportion of patients with elevated blood lipids was lower in the tacrolimus group than in the placebo group. There were no notable trends in vital signs or abnormal ECG findings over time or differences between the treatment groups. In addition there were no notable differences in weight or BMI change from baseline between the treatment groups.

Date of Report: 26 Sep 2014