2. SYNOPSIS

Name of Sponsor/Company: Ono Pharma USA, Inc. (a subsidiary of Ono Pharmaceutical Co., Ltd., Osaka, Japan)	Individual Study Table Referring to Part of the Dossier Volume: Page:	*(For National Authority Use Only)*
Name of Finished Product: ONO-4641		

Title of Study: A Double-Blind, Placebo-Controlled, Single Dose Escalation and Food Effect Study to Evaluate the Safety, A Double-Blind, Placebo-Controlled Study of the Safety and Efficacy of ONO-4641 in Patients with Relapsing-Remitting Multiple Sclerosis	
Study centers: 95 sites in North America, Europe, and Asia	
Publications (reference): None	
Studied period (years): Date first subject enrolled: 12 March 2010 Date last subject completed: 29 November 2011	**Phase of development:** 2
Objective: The objective of the study was to evaluate the safety and efficacy of ONO-4641 at potentially therapeutic doses in patients with relapsing-remitting multiple sclerosis (RRMS) over a 26-week treatment period.	
Methodology: The study was a double-blind, randomized, placebo-controlled, safety and efficacy multicenter study in patients with RRMS consisting of a Screening Period of up to 28 days, a 26-week Treatment Period, and a 4-week Follow-up Period. The planned enrollment was for approximately 376 patients. While 593 patients were screened, 186 failed screening procedures, and 407 patients were randomized.	

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Methodology, continued:

Eligible patients had predose evaluations on Day 1 to collect baseline data. Patients were randomly assigned 1:1:1:1 via an interactive voice response system (IVRS) to the placebo, 0.05 mg, 0.10 mg, or 0.15 mg of ONO 4641 treatment groups, and each treatment group of approximately 101 patients received their respective dose once per day (qd) for 26 weeks. There were 8 visits during the Treatment Period, spaced 4 weeks apart except for the second treatment visit (Visit 3), which was 2 weeks after the initial dose. The primary endpoint was the cumulative number of T1 weighted gadolinium (Gd)-enhanced lesions obtained with MRI at Weeks 10, 14, 18, 22, and 26. Patients who completed the treatment period or who discontinued during the treatment period and did not proceed to the extension study entered the 4-week Follow-up Period.

Patients were monitored throughout the study period at regularly scheduled visits to the investigational site. Safety monitoring consisted of physical examinations, recording of vital signs, periodic recording of 12-lead electrocardiograms (ECGs), pulmonary function tests (PFTs), clinical laboratory tests, comprehensive ophthalmic examinations including optical coherence tomography (OCT), dermatological examinations, MRI imaging, relapse surveillance, EDSS rating, and surveillance for AEs and concomitant medications. In addition, diffusion capacity of lung for carbon monoxide (DLCO), Holter monitoring and lymphocyte subset analyses were performed at selected sites.

Blood samples for plasma pharmacokinetic (PK) assessment were collected during the Treatment Period. Surveillance of adverse events (AEs) began with dose administration and continued throughout the study. If no ongoing clinical or laboratory AEs were present at the last follow-up visit, the subject was discharged from the study. Otherwise, continued follow-up until resolution or stabilization of the AE occurred at the discretion of the investigator. Patients with ongoing clinically significant AEs on the day of discharge were followed until 30 days after dosing.

Number of patients (planned and analyzed):

Planned: 376 patients; 593 patients screened; 407 patients randomized

Analyzed: 404 patients for Safety Set; 401 patients for Full Analysis Set; 356 patients for Per Protocol Set

Patients received ONO-4641 (0.05, 0.10, 0.15 mg) or placebo in a 1:1:1:1 ratio.

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Diagnosis and main criteria for inclusion: Male and female patients with RRMS aged 18 to 55 years with an EDSS score between 0 and 5.5, stable neurological condition (relapse-free for at least a month prior to and during screening and at baseline), and a positive antibody enyzyme-linked immunosorbent assay (ELISA) for varicella zoster virus (chicken pox),who provided written informed consent for participation. Patients also had to meet the following criteria:

a. At least 2 documented relapses within 2 years prior to screening; OR

b. At least 1 documented relapse within the year prior to screening; OR

c. At least 1 Gd-enhanced lesion detected on locally read MRI within 3 months prior to randomization (Visit 2).

Females had to test negative for pregnancy at both screening and study admission; females had to be surgically sterile or postmenopausal or, if of childbearing potential, then had to be nonlactating and, if sexually active, had to agree to use an acceptable form of birth control from 1 month prior to the first dose until 2 months after the last dose. Males had to be surgically sterilized or agree to the use of a double-barrier method from 2 weeks before initiation of study drug administration until 2 months after the last dose. Males also agreed to refrain from sperm donation from the initiation of study drug administration until 2 months after the last dose. All patients had to test negative for human immunodeficiency virus (HIV) and hepatitis B (HBsAg)and C (HCV).

Test product, dose and mode of administration, batch number:

0.05 mg, 0.10 mg, and 0.15 mg dosage strengths for oral administration

Lot X015P for all patients in Japan. For all patients who enrolled in North America and Europe, Lot X9Y1P was dispensed for Visit 2 and Lot X9Y2P was dispensed for all other visits.

Duration of treatment: 26 weeks

Reference therapy, dose and mode of administration, batch number:

Matching placebo tablet for oral administration.

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Criteria for evaluation:

Efficacy: The primary endpoint was the cumulative number of T1-weighted Gd-enhanced lesions obtained with MRI at Visits 5 to 9 (Weeks 10, 14, 18, 22 and 26). The secondary endpoints included the total number of T1-weighted Gd-enhanced lesions obtained with MRI at 4-week intervals for 26 weeks, the cumulative volume of Gd-enhanced lesions, the total number of new or enlarging T2 lesions, change in T2 lesion volume, change in brain volume, the proportion of patients with Gd-enhanced lesions, the number of patients remaining free of relapse, annualized relapse rate, the time to the first relapse, and the change from baseline in EDSS scores.

Pharmacokinetics: The plasma concentration of ONO-4641 was calculated.

Pharmacodynamics (PD): The PD of ONO-4641 was studied by evaluation of white blood cell (WBC) differential count (for all patients) and lymphocyte subsets (for patients at selected sites).

Safety: Safety and tolerability assessments included AEs, clinical laboratory evaluations (hematology, coagulation, serum chemistry, and urinalysis), concomitant medications, PFTs, comprehensive ophthalmic examinations including OCT, dermatological examinations, MRI imaging, relapse surveillance, EDSS rating, 12-lead ECGs, vital signs, and physical examination. DLCO, Holter monitoring, and lymphocyte subset analyses were performed for a subgroup of patients.

Statistical methods:

Efficacy: Both the Full Analysis Set (FAS) and Per Protocol Set (PPS) were used for the analysis of efficacy, which included 2 subgroups in North America/Europe and Japan. The PPS was the primary analysis population for the primary efficacy endpoint (cumulative number of T1-weighted Gd-enhanced lesions obtained with MRI at Visits 5 to 9). The descriptive statistics were presented by treatment group and a nonparametric Wilcoxon rank-sum test was performed to compare each ONO-4641 treatment group with the placebo group. The FAS was used for the sensitivity analysis of the primary endpoint.

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Statistical methods continued:

Pharmacokinetics/Pharmacodynamics: The arithmetic mean and standard deviation of plasma ONO-4641 concentration and the elapsed time since the latest administration of ONO-4641 were calculated for each treatment group and for specific visits (Visit 3, 6, 9, or Early Termination). These values were also summarized by region: Japan and North America-Europe.

Safety: Patients in the Safety Set were used for safety and tolerability assessments including the reporting of AEs, clinical laboratory evaluations, vital sign measurements, physical examinations, spirometry, DLCO, MRI, ophthalmic examination, and 12-lead ECG data. Data were presented using summary statistics and subgroup analyses for North America/Europe and Japan were performed on selected safety parameters.

The number and percentage of subjects with AEs, SAEs, treatment-related AEs, and AEs by severity were summarized by treatment group. Clinical laboratory, vital signs, and 12-lead ECG data were summarized by treatment group using descriptive statistics. Shift tables by treatment group and study day were presented for clinical laboratory data. Maximum change in the QT/QTc interval, i.e., the maximum observed postbaseline QT/QTc values and the maximum change from baseline in QT/QTc intervals were summarized. The proportion of subjects who had maximum absolute QT and QTc intervals of ≤450 ms, >450 to ≤480 ms, >480 to ≤500 ms, and >500 ms were presented. The proportion of subjects who had a maximum change from baseline in QT and QTc intervals of ≤30 ms, >30 to ≤60 ms, and >60 ms were presented.

SUMMARY – CONCLUSIONS

There were 407 male and female subjects randomized into 4 dose cohorts (0.05, 0.10, 0.15 mg ONO-4641 and placebo). The majority of the RRMS patients was Caucasian, with an age range of 18 to 55 years, and had an average of 2.0 relapses during the 2 years prior to the study. Patients were predominantly female, non-Hispanic, and White.

PHARMACOKINETIC RESULTS:

The mean of the plasma concentration of ONO-4641 increased with dose strength.

PHARMACODYNAMIC RESULTS:

As expected, peripheral ALC decreased with increasing dose level. Study results showed that the average ALC was reduced in a dose-dependent manner to 1,160 cells/μL (approximately 40% reduction from baseline) in the 0.05 mg cohort, 680 cells/μL (approximately 60% reduction from baseline) in the 0.10 mg cohort, and 590 cells/μL (approximately 65% reduction from baseline) in the 0.15 mg cohort. These results suggest that even a 40% reduction in lymphocyte count is associated with positive MRI outcomes.

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EFFICACY RESULTS:

The cumulative number of T1-weighted Gd-enhanced lesions from Week 10 to Week 26 was significantly lower in all 3 ONO-4641 treatment groups compared to placebo ($p<0.0001$). Following are the secondary endpoint results:

1. The cumulative number of T1-weighted Gd-enhanced lesions from all postbaseline visits was significantly lower in all 3 ONO-4641 treatment groups compared to placebo ($p<0.0001$).
1. At Week 26, the 0.10 mg and 0.15 mg treatment groups had statistically fewer and smaller T1-weighted Gd-enhanced lesions compared to placebo ($p=0.0291$ and $p=0.0430$, respectively).
2. The cumulative number of new or enlarged T2 lesions was significantly reduced ($p<0.0001$), with reductions of 73%, 81%, and 71% at the 0.05, 0.10, and 0.15 mg doses, respectively, compared to placebo.
3. All 3 treatment groups had significant reductions in the number of new or enlarged T2 lesions compared to the placebo group ($p<0.0001$).
4. All 3 treatment groups achieved statistical significance versus placebo by Week 26 for change from baseline of T2 lesion volume ($p=0.0011$, $p=0.0043$, $p=0.0010$ for the 0.05, 0.10, and 0.15 mg treatment groups, respectively).
5. All 3 active treatment groups had significantly fewer patients with postbaseline lesions than the placebo group in the proportion of patients with Gd-enhanced lesions ($p<0.0001$).
6. Only the 0.10 mg treatment group was statistically significant compared to placebo ($p=0.0069$) for the annualized relapse rate. The study was not powered for relapse endpoints.
7. Time to first relapse was significantly longer in the 0.10 mg treatment group when compared to placebo ($p=0.0069$).
8. The 0.10 mg treatment group was statistically significant from the placebo group ($p<0.0005$) while the 0.15 mg treatment group trended towards significance ($p=0.0695$) for the proportion of patients remaining free from relapse.
9. Although the study was not powered for change from baseline in overall EDSS scores, the 0.10 mg treatment group trended towards significance ($p=0.0957$).

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SAFETY RESULTS:

Overall, 1471 AEs were recorded in 404 subjects. Most of the AEs were mild or moderate and approximately half were considered to be related to study medication in all 4 treatment groups. Seventeen AEs were assessed by the investigator as severe AEs. There were no deaths, and 36 patients had 47 SAEs during the study. Ten patients met the stopping rule of elevated LFTs and therefore discontinued study treatment. Three patients had an AE leading to withdrawal during the study: mild intermittent nausea, moderate prolonged QT, and reaction to contrast medium for MRI testing. Adverse events of special interest (AESIs) were monitored during the course of the study based on data from the 5 Phase 1 studies of ONO-4641 and a similar S1P agonist. They include cardiovascular, vascular, eye, respiratory, and gastrointestinal disorders, infections, and increases in liver function tests. Based on this 26-week study, ONO-4641 is associated with transient, decreased heart rate, increased alanine transaminase (ALT) / aspartate transaminase (AST), and dose-dependent lymphocyte suppression. The 10 discontinuations due to a stopping rule were all related to increased liver function tests (LFTs) which trended towards the normal range within 1 to 8 months after study discontinuation. The decrease in heart rate of the 3 progressive doses of ONO-4641 compared to placebo appeared to be dose-dependent and dissipated by Day 183. Most cardiac events occurred on Day 1 from 2 to 4 hours postdose but some cardiac rhythm disturbances occurred later throughout the study. The findings of this study suggest that ONO-4641 is associated with First Degree AV block, Second Degree AV block (Mobitz Type I), Wandering Atrial Pacemaker, non-sustained SVT and VT, and dose-dependent sinus bradycardia.

One case of maculopathy was confounded by pre-existing, predisposing ocular abnormalities. The occurrence of macular oedema must be monitored in larger trials to determine with more certainty whether or not ONO-4641 can cause macular oedema. Gastrointestinal disorders were more commonly reported with ONO-4641 than with placebo. Gastrointestinal disorders occurring in more than 2% of the patients include abdominal discomfort, abdominal pain, constipation, diarrhoea, flatulence, nausea, and vomiting. The 0.05 mg and 0.15 mg treatment groups had a mean decrease in FEV_1 of 3% at Week 26, which is indicative of mild bronchoconstriction. The overall rate of infection was similar in all 4 groups. However the incidence of non-disseminated herpes was higher in the 0.05 and 0.10 mg treatment groups than in the placebo and 0.15 mg groups. One case of Herpes zoster oticus in the 0.15 mg treatment group was reported as an SAE that resolved with sequelae.

CONCLUSION:

ONO-4641 demonstrated significant efficacy when compared to placebo and was well tolerated by the study population of RRMS patients with no unexpected AEs. The ongoing, open-label, extension Study ONO 4641POU007 will provide long-term safety and efficacy data with up to 122 weeks of

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Date of the report: 24 January 2013		