2 SYNOPSIS

Name of Sponsor/Company:		**Protocol No.: MS-LAQ-301**
Teva Pharmaceutical Industries, Ltd., POB 8077, Sapir Industrial Zone, Kiryat Nordau, Netanya 42504, Israel		
Code Name of Finished Product:		
TV-5600 (previously ABR-215062)		
Name of Active Ingredients:		
Laquinimod sodium		
Study Title A multinational, multicenter, randomized, double-blind, parallel-group, placebo-controlled study, to evaluate the safety, tolerability and efficacy of daily oral administration of laquinimod 0.6 mg in subjects with relapsing remitting multiple sclerosis (RRMS).		
Study Principal Investigators Prof. Giancarlo Comi U.O.Neurology – Neurorehabilitation and Clinical Neurophysiology Fondazione Centro San Raffaele del Monte Tabor Via Olgettina 48 – 20132 Milano, Italy		
MRI Principal Investigator Prof. Massimo Filippi Neuroimaging Research Unit Dept. of Neurology, Ospedale San Raffaele Via Olgettina 60 20132 Milano, Italy		
Study Site Investigators and Respective Study Sites See Appendix 16.1.4.		
Publication Based on Study Results		
Study Dates	13/11/2007-08/11/2010	**Clinical Phase** III
Test Drug, Dose and Mode of Administration, Batch Number Laquinimod sodium, 0.6 mg, oral. Batch number: see Appendix 16.1.6. **Reference Drug, Dose and Mode of Administration, Batch Number** Matching placebo. Batch number: see Appendix 16.1.6.		
Objectives The study objective was to assess the efficacy, tolerability and safety of daily oral administration of laquinimod 0.6 mg in subjects with RRMS. The primary objective was to assess the efficacy of a daily dose of laquinimod 0.6 mg compared to placebo, as measured by the number of confirmed relapses during the 24-month double blind study		

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period.

The secondary objectives were:

- To compare the cumulative number of enhancing lesions on T_1-weighted images taken on Months 12 and 24 (termination/early discontinuation visit after Month 12) between the laquinimod 0.6 mg and the placebo groups.
- To compare the cumulative number of new (hyperintense) T_2 lesions on scans taken on Months 12 and 24 (termination/early discontinuation visit after Month 12) between the laquinimod 0.6 mg and the placebo groups.
- To compare the accumulation of physical disability as measured by the time from randomization to confirmed progression of EDSS during the 24-Month double blind study period, between laquinimod 0.6 mg and the placebo groups.
- To compare the disability as assessed by the MSFC score at Month 24 (termination/early discontinuation visit after Month 12) between the laquinimod 0.6 mg and the placebo groups.

Methodology

This was a multinational, multicenter, randomized, double-blind, parallel-group, placebo-controlled study, to evaluate the efficacy, tolerability and safety of daily oral administration of laquinimod 0.6 mg in RRMS subjects.

Eligible subjects were equally randomized into one of the following treatment arms:

- Laquinimod capsules 0.6 mg
- Placebo for laquinimod capsules 0.6 mg

Subjects were evaluated at study sites for 12 scheduled visits at months: -1 (screening), 0 (baseline), 1, 2, 3, 6, 9, 12, 15, 18, 21 and 24 (termination/early discontinuation study).

Either two separate Neurologists or two Physicians assessed the subjects. An Examining Neurologist/Physician assessed the subject's neurological examination, unaware of subject's well-being; and a Treating Neurologist/Physician decided whether a subject experienced a relapse and prescribed steroids or other concomitant medications as needed.

Number of Subjects (total and for each treatment): 1106 subjects; 550 on laquinimod 0.6 mg and 556 on placebo.

Diagnosis and Main Criteria for Inclusion

Inclusion:

Subjects had to meet all inclusion criteria in order to be eligible for the study:

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- Males and females between 18 and 55 years of age, inclusive.

- Subjects had to have a confirmed and documented MS diagnosis as defined by the Revised McDonald criteria with a relapsing-remitting-disease course.
- Subjects had to have had experienced one of the following:
  - At least one documented relapse in the 12 months prior to screening.
  - At least two documented relapses in the 24 months prior to screening.
  - One documented relapse between 12 and 24 months prior to screening with at least one documented T_1-Gd enhancing lesion in an MRI performed within 12 months prior to screening.
- Subjects had to have disease duration of at least 6 months (from the first symptom) prior to screening.
- Subjects had to be ambulatory with converted Kurtzke EDSS score of 0-5.5.
- Subjects had to be in a stable neurological condition and free of corticosteroid treatment [intravenous (iv), intramuscular (im) and/or per os (po)] 30 days prior to screening (Month -1).
- Women of child-bearing potential had to practice an acceptable method of birth control.
- Subjects had to be able to sign and date a written informed consent prior to entering the study and to be willing and able to comply with the protocol requirements for the duration of the study.

Exclusion:

Any of the following conditions excluded the subject from entering the study:

- Subjects with progressive forms of MS.
- An onset of relapse, unstable neurological condition or any treatment with corticosteroids or ACTH between screening and baseline.
- Previous treatment with glatiramer acetate (GA), Interferon-β (IFNß) (either 1a or 1b), Intravenous Immunoglobulin (IVIG), or systemic chronic corticosteroid treatment (30 or more consecutive days) within 2 months prior to screening visit.
- Use of experimental or investigational drugs, and/or participation in clinical studies, or use of immunosuppressive (including Mitoxantrone (Novantrone®) or cytotoxic agents within the 6 months prior to screening visit.
- Use of amiodarone within 2 years prior to screening visit.

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- Previous use of either of the following: natalizumab, (Tysabri®), cladribine or laquinimod.
- Previous total body irradiation, total lymphoid irradiation, stem cell treatment, autologous or allogenic bone marrow transplantation.
- A known history of tuberculosis.
- Acute infection within two weeks prior to baseline visit.
- Major trauma or surgery within two weeks prior to baseline.
- Use of inhibitors of CYP3A4 (Cytochome P) within 2 weeks prior to baseline visit (1 month for fluoxetine).
- Pregnancy or breastfeeding.
- A ≥3xULN serum elevation of either ALT or AST at screening or serum direct bilirubin which is ≥2xULN at screening.
- A QTc interval which is ≥ 450 msec (according to machine output), obtained from (2 ECG recordings at screening visit, or the mean value calculated from 3 baseline ECG recordings).
- Subjects with a clinically significant or unstable medical or surgical condition that would preclude safe and complete study participation, as determined by medical history, physical exams, ECG, abnormal laboratory tests or chest X-ray.
- A known history of sensitivity to Gd.
- Inability to successfully undergo MRI scanning.
- Known drug hypersensitivity that would preclude administration of laquinimod, such as hypersensitivity to: mannitol, meglumine or sodium stearyl fumarate.

Duration of Treatment

This double-blind placebo-controlled study was planned for 24 months. A blinded variance analysis of the population progression rate and power reassessment was planned prior to first-patient completion of the 24 months double blind period (as defined in the protocol), to determine the need for extending the double blind study duration to 30 months in order to enhance the probability of meeting the disability secondary end point. The reassessment was performed on July 27, 2009. The results of this assessment, according to the pre-defined decision rule, lead to the decision to end the study, at the end of 24 months of treatment and not to extend it to 30 months.

Subjects successfully completing the study were offered the opportunity to enter an open label extension phase (MS-LAQ-301E) in which they would be receiving laquinimod 0.6 mg until

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laquinimod 0.6 mg is commercially available or development of laquinimod 0.6 mg for MS is stopped by the Sponsor.	

Criteria for Evaluation

Efficacy Measures:

Primary Endpoint:

The total number of confirmed relapses observed during the double-blind treatment period as a mechanism for estimating the treatment effect on the annualized relapse rate. The primary analysis was aimed at the comparison of the annualized relapse rate between the 0.6 mg laquinimod arm and the placebo arm.

Secondary Endpoints

Comparison of laquinimod 0.6 mg and placebo groups in:

- The cumulative number of Gd-enhancing lesions on T_1-weighted images taken on Months 12 and 24 (termination/early discontinuation visit after Month 12).
- The cumulative number of new/enlarging (hyperintense) T_2 lesions on scans taken on Months 12 and 24 (termination/early discontinuation visit after Month 12).
- Accumulation of physical disability measured at the time of confirmed progression of EDSS. Progression was defined as at least 1 point increase from baseline on EDSS score if baseline EDSS was between 0 and 5.0, or at least 0.5 point increase if baseline EDSS was 5.5 or higher, confirmed 3 months later. Progression could not be confirmed during an MS relapse.
- Disability as assessed by the MSFC score at Month 24 (termination/early discontinuation visit after Month 12).

Exploratory Endpoints:

- The time to the first confirmed relapse during the study period.
- The rate of confirmed relapses during the study period, requiring hospitalization and/or IV steroids.
- The proportion of relapse free subjects.
- The total volume of (hyperintense) T_2 lesions at Month 12.
- The total volume of (hyperintense) T_2 lesions at Month 24 (termination/early discontinuation visit after Month 12).
- The total volume of hypointense lesions on enhanced T_1 scans at Month 12.

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- The total volume of hypointense lesions on enhanced T1 scans at Month 24 (termination/early discontinuation visit after Month 12).
- Brain atrophy as defined by the percentage change in normalized brain volume from baseline to Month 12.
- Brain atrophy as defined by the percentage change in normalized brain volume from baseline to Month 24 (termination/early discontinuation visit after Month 12).
- Disability as assessed by MSFC at months 6, 12, and 18.
- The cumulative number of new hypointense lesions on enhanced T1 scans at Months 12 and 24 (termination/early discontinuation visit after Month 12).
- Subject-reported fatigue as assessed by the Modified Fatigue Impact Scale (MFIS) at Month 24 (termination/early discontinuation visit after Month 12).
- General health status by the EuroQoL (EQ5D) questionnaire at Month 24 (termination/early discontinuation visit after Month 12).
- The general health status, assessed by the Short-Form general health survey (SF-36) subject-reported questionnaire change from baseline to Month 24 (termination/early discontinuation visit after Month 12).
- Binocular low-contrast visual acuity assessment, using 100%, 2.5% and 1.25% contrast charts.
- Results of population PK analysis will be included in a separate report.

Statistical Methods

Data analysis sets for efficacy :

- Intent-To-Treat Analysis Set (ITT): Consists of all subjects who have been randomized. In accordance with the ITT principle, all subjects randomized were kept in their originally assigned treatment group. This analysis set serves as the principal analysis set for the primary analysis inference.
- Completers Analysis set (CO): Consists of all subjects who completed the 24 months of double-blind treatment.
- Evaluable Analysis Set (EV): This is a subset of the Completers analysis set. It consists of all subjects in the CO analysis set who complied with major protocol.

Assignment to the analysis sets was performed before revealing the study blind for the final analysis.

An additional analysis set was defined for analyses of safety data:

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- Safety Analysis Set (ST): Consists of all subjects who have been randomized and received at least one dose of STUDY DRUG.

Level of Significance

The overall significance level for this study is 5% using two-tailed tests and/or two-sided confidence intervals with 95% confidence level.

In order to protect the study from type-I error inflation, the secondary endpoints were interpreted inferentially only if a statistically significant treatment effect was detected in the primary analysis.

The study's overall type-I error was further controlled in the analysis of the secondary endpoints by applying the following gate-keeping procedure:

The first two MRI-based secondary endpoint were analyzed simultaneously with an overall type-I error of 5%, using the Hochberg's step-up modification to Bonferroni's method to the two p-values obtained from the analyses of these two endpoints.

The third secondary endpoint, accumulation of physical disability measured by the time to confirmed progression of EDSS was to be interpreted inferentially only if at least one of the 2 endpoints analyzed in the first step of the secondary analysis was significant under Hochberg's procedure.

The fourth secondary endpoint, disability as assessed by MSFC was to be interpreted inferentially only if the accumulation of physical disability endpoint analyzed in the second step of the secondary analysis was significant.

Primary Endpoint

The principal statistical analysis of the annualized relapse rate during study was performed on the ITT cohort and was based on the outcome of a contrast (laquinimod 0.6 mg vs. placebo) derived from a baseline-adjusted, quasi-likelihood (over-dispersed) Poisson regression (SAS® PROC GENMOD with DIST=POISSON and DSCALE options). Subject's number of relapses during the double blind placebo controlled phase served as the response variable.

An offset based on the log of subject's exposure in years was employed to adjust for variability of treatment exposure. In addition to the treatment group, the model included the covariates: baseline EDSS score, log of prior 2-year number of relapses+1 and country or geographical region (CGR).

The robustness of the results obtained by the principal analysis was explored by applying the principal model (Poisson regression) on CO and EV analysis sets. Additional models, negative binomial and ANCOVA (with and without covariates) and the Wilcoxon rank-sum test were applied to the ITT analysis set.

Secondary Endpoints

Analyses of the two MRI endpoints, the cumulative number of Gd-enhancing lesions on T_1-weighted

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images and the cumulative number of New/Enlarging T_2 lesions were tested simultaneously, each employing the negative binomial regression model (SAS® PROC GENMOD). An offset based on the log of relative exposure in the study (actual exposure (years)/2 years) was employed to adjust for early termination's lack of exposure. In addition to the treatment group, the model included the number of T_1 Gd-enhancing lesions at baseline and CGR as covariate, for both endpoints and in addition the baseline T_2 volume for the new/enlarging T_2 count endpoint.

The third endpoint, time to EDSS progression confirmed after 3 months, was analyzed based on Cox Proportional Hazard model (SAS® PROC PHREG). The inference was based on the 95% confidence limit for the hazards ratio of the treatment (using the RISKLIMITS option of the MODEL statement). The model also included baseline EDSS, log of the (prior 2-year number of relapses +1) and CGR as covariates.

The fourth endpoint, disability as assessed by the MSFC score at Month 24 (termination/early discontinuation visit after Month 12), was analyzed based on Analysis of Covariance (SAS® PROC GLM), with baseline MSFC, baseline EDSS, log of the (prior 2-year number of relapses +1) and CGR as covariates.

Summary of Results

Patient Disposition

A total of 1,106 subjects were randomized to the study; 550 subjects randomized to laquinimod 0.6 mg and 556 subjects to placebo. The study was conducted in 21 European countries, in Israel and in North America (USA and Canada).

Overall, 864 subjects completed the study according to protocol: 437 (79.5%) in the laquinimod 0.6 mg treatment group and 427 (76.8%) in the placebo group. A total of 242 subjects prematurely terminated from the study: 113 (20.5%) on laquinimod 0.6 mg and 129 (23.2%) on placebo. Subjects who prematurely terminated from the study, were invited to a follow-up visit a month later.

The most common reasons for early withdrawal from the study were due to AEs (7.6% on laquinimod 0.6 mg and 5% on placebo), and withdrawal of consent (5.8% on laquinimod 0.6 mg and 6.8% on placebo). Time since first symptom 8.6 ± 6.7 years on placebo and 8.7 ± 6.9 years on laquinimod 0.6 mg; time since diagnosis was 5.0 ± 5.2 and 5.2 ± 5.1 years on placebo and laquinimod, respectively. Number of exacerbations in the 1-year prior to study was 1.3 ± 0.7 and 1.2 ± 0.7 on placebo and laquinimod, respectively, and in the 2 years prior to study was 1.9 ± 1.0 in both groups. Baseline EDSS (converted) was 2.6 ± 1.3 in both groups. Overall, 39% of the subjects used MS medications prior to study entry including immunomodulators, immunosupressants, antineoplastic agents and immunoglobulins. Baseline MRI parameters were comparable between the groups.

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Efficacy Results

Primary endpoint

Results of the principal analysis of the primary endpoint, the annualized relapse rate during the double-blind placebo controlled treatment period, demonstrated a statistically significant benefit with treatment of laquinimod 0.6 mg over placebo, with a Risk Ratio [95% CI] = 0.770 [0.650; 0.911, p-value=0.0024, reflecting a reduction of 23% in the risk for confirmed relapse based on the principal analysis model. This analysis employed the baseline-adjusted, quasi-likelihood (over-dispersed) Poisson regression on the ITT analysis set.

The robustness of the results obtained by the principal analysis was explored by applying the principal model (Poisson regression) on CO and EV analysis sets. Additional models, negative binomial and ANCOVA (with and without covariates) and the Wilcoxon rank-sum test were applied to the ITT analysis set. An analysis performed *post-hoc* on the dropouts as well as missing data imputation models showed similar results to that of the principal analysis, implying that the results obtained for the primary endpoint were not appreciably impacted by missing data.

Secondary endpoints

Four secondary endpoints were analyzed based on a hierarchical approach. The first two endpoints that were MRI-based were tested simultaneously: The cumulative number of T_1 Gd-enhancing lesions at Months 12 and 24 (Termination/Early Discontinuation visit after Month 12) and the cumulative number of New/Enlarging T_2 lesions. Both were analyzed using negative binomial regression adjusting for exposure and covariates.

A statistically significant effect of laquinimod 0.6 mg over placebo was demonstrated for both endpoints. For the cumulative number of T_1 Gd-enhancing lesions: Rate Ratio [95% CI] = 0.629 [0.488; 0.809], p-value=0.0003, reflecting a reduction of 37% the mean rate of developing T_1 Gd-enhancing lesions on laquinimod 0.6 mg compared to placebo. For the cumulative number of New/Enlarging T_2 lesions: Rate Ratio [95% CI] = 0.704 [0.584; 0.849], p-value=0.0002, reflecting a reduction of 30% in the mean rate of developing New/Enlarging T_2 lesions on laquinimod 0.6 mg compared to placebo.

The third secondary endpoint in the hierarchy was time to confirmed progression of EDSS, sustained for 3 months. The results based on the Cox proportional hazards model showed a statistically significant treatment effect of laquinimod 0.6 mg over placebo: Hazard Ratio [95% CI] = 0.641 [0.452; 0.908], p-value=0.0122. This result demonstrates that laquinimod 0.6 mg reduced the risk for confirmed progression of EDSS by 36% compared to placebo, and delayed the time to disability. An additional analysis *(post-hoc)* for progression of EDSS, sustained for 6 months showed an effect of 48% on treatment with laquinimod.

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The fourth secondary endpoint, disability assessed by MSFC at Month 24 (termination/early discontinuation visit after Month 12), did not a show statistically significant difference between the groups. It should be noted that the changes from baseline reflected by the Z-scores were of a very small magnitude in both groups and especially in placebo, making it hard to detect differences between treatments

Exploratory endpoints

Among the exploratory endpoints, an effect of treatment with laquinimod 0.6 mg over placebo was shown for the relapse-related endpoints of time to first relapse, proportion of relapse-free subjects and rate of severe confirmed relapse.

For MRI-based endpoints, treatment with laquinimod 0.6 mg showed reduction in brain atrophy over placebo at Months 12 and 24, as well as benefit for treatment with laquinimod 0.6 mg over placebo in the cumulative number of new/enlarging hypointense lesions.

No appreciable difference between laquinimod and placebo could be shown at Months 12 or 24 for the T_2 lesions volume or hypointense lesions volume. It should be noted that the change from baseline in these volumes for the placebo group were of very small magnitude, thus, not enabling a detection of effect.

Treatment with laquinimod 0.6 mg was, on average, associated with less functional disability due to fatigue than for placebo treated subjects. The general health status assessed by the 5 dimension Euro-QOL Questionnaire (EQ-5D), was mainted for laquinimod-treated subjects, while a decline in health status was reported by the placebo subjects. For the SF-36 subject-reported questionnaire: in both, the Physical component summary score and the Mental component summary score subjects treated with laquinimod 0.6 mg remained stable while the score for those treated with placebo declined. No appreciable difference between laquinimod and placebo could be demonstrated in visual acuity.

Safety Results

Extent of Exposure

Of the total of 1,106 subjects who participated in the clinical study MS-LAQ-301 (ALLEGRO), 550 were exposed to laquinimod 0.6 mg for 965.6 subject years and a total of 556 subjects received placebo for 953.3 subject years. Mean exposure was similar across treatment groups (laquinimod 0.6 mg vs. placebo 20.9±6.3 months vs. 20.4±6.7 months). Most subjects (75.5% on laquinimod 0.6 mg and 72.7% on placebo) were exposed between 21 and 24 months.

Adverse Events

Common AEs were defined as AEs reported by 5% or more in any treatment group. Common AEs by PT reported by 5% or more of subjects in the laquinimod group and with an incidence higher than in the placebo group by at least 1% were: headache (22.7% vs. 17.8%), back pain (16.4% vs. 9%),

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diarrhea (8 % vs. 6.1%),cough (7.5% vs. 4.5%), urinary tract infection (7.3% vs. 4.5%) and ALT increased (6.9% vs. 2.7%; see below for detailed analysis of laboratory data). None of these AEs showed a hazard rate pattern suggestive of exposure-dependence; hazard rate was highest up to 6 months from first dose and the added exposure did not increase the rate.

In addition, the following HLT and HLGTs were also reported by at least 5% of laquinimod treated subjects and with an incidence higher than in the placebo group by at least 1%: gastrointestinal and abdominal pains (excluding oral and throat) (11.1% vs. 8.8%) and menstrual cycle and uterine bleeding disorders (7.8% vs. 4.9%).

No laquinimod-treated subjects died during the study; 2 placebo-administered subjects died during the study (one due to a train accident and the other committed suicide) and a third placebo subject died following termination due to complications of pneumonia that started during the study.

Other SAEs were reported with a comparable incidence but slightly higher in the laquinimod 0.6 mg group. No specific SAE came up as a safety signal of concern. The SAE reported with the highest incidence was appendicitis, reported by 5 subjects (0.9%) in the laquinimod 0.6 mg group compared to 1 subject (0.2%) in the placebo group. SAEs of liver function analyses were reported by 2 subjects (0.4%) on laquinimod 0.6 mg vs. none on placebo. Of note, SAEs of MS relapse were reported with a higher incidence in the placebo group.

Incidence of subjects terminating due to AEs was higher in the laquinimod 0.6 mg group (7.6% vs. 5%). AEs of elevated liver enzymes (ALT increased (1.1% vs. 0.4%), AST and GGT increased (0.5% vs. 0.2% each) and transaminases increased (0.4% vs. 0.2%); see below for detailed analysis of laboratory data) were among the ones leading to early termination with a higher incidence in the laquinimod 0.6 mg group than placebo. This is in accordance with the study's protocol defined safety stopping rules. Of note, AEs of liver disorder led to the early termination of 2 subjects in the placebo group and none in the laquinimod 0.6 mg group. Other AEs leading to early termination with a higher incidence in the laquinimod 0.6 mg group than the placebo group included AEs of abdominal pains (abdominal pain (0.5% vs.0.2%) and abdominal pain upper (0.9% vs.0)) and diarrhoea (0.5% vs.0).

In depth analysis of liver safety yielded only laboratory-related AEs as a safety signal for laquinimod (mainly elevated liver transaminases; see below for detailed analysis of laboratory data).

SAEs of malignancies were evenly distributed between the laquinimod 0.6 mg and the placebo group; malignant breast neoplasms were reported by 3 subjects, 0.5% on laquinimod 0.6 mg vs. 1 subject (0.2%) on placebo while SAEs of ovarian, prostate and rectal malignancies were reported by subjects in the placebo group only. One of the laquinimod-treated subjects had a medical history of ipsilateral breast cancer; bringing the total number of treatment-emergent AEs of this HLT to 2 on laquinimod and 1 on placebo. The number of reports of malignant breast neoplasms is low and does not allow drawing any conclusions about possible effects of the drug.

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Incidence of AEs of the SOC Infections and Infestations was similar across treatment groups and no specific type of infecting organism came up as a safety signal of concern.

No cases of pericarditis or pleuritis were reported during the study. The HLGTs acute and chronic pancreatitis and ischaemic coronary artery disorders were each reported by 2 subjects in the laquinimod 0.6 mg group and by 1 subject in the placebo group. Arthritis was reported by 4 subjects in the laquinimod 0.6 mg group and by 1 subject in the placebo group.

Severe AEs were reported with a similar but slightly higher incidence in the laquinimod 0.6 mg group. Headache, back pain, migraine, cellulitis, chest pain, dizziness, hypokalaemia and renal colic were reported as severe with a higher incidence in the laquinimod 0.6 mg group.

AEs with sequelae were reported with similar incidence across treatment groups. The incidence of AEs assessed by the investigators as possibly related to study drug was higher in the laquinimod 0.6 mg group. In the laquinimod 0.6 mg group, the AEs assessed by the investigator as related to study drug with the highest incidence were ALT increased and GGT increased.

Overall incidence of AEs was similar between genders across treatment groups. Contrary to the study population as a whole, the PT ALT increased did not represent a safety signal among laquinimod treated female subjects; it was reported by 4 times as many laquinimod-treated males as laquinimod-treated females. It is worth noting that incidence of laquinimod-treated males reaching PCS levels of ALT was approximately 3 times higher than that of laquinimod-treated females.

In the region of USA and Canada, incidence of AEs was identical between treatment groups and in the rest of the world, incidence was higher in the laquinimod 0.6 mg. Overall incidence of AEs, SAEs and early termination due to AEs were higher in laquinimod-treated subjects located in the USA and Canada than in laquinimod treated subjects in the rest of the world. Incidence of SAEs and early termination due to AEs were higher in laquinimod-treated subjects located in the USA and Canada than in placebo-administered subjects of the same region. In the region of the rest of the world, incidence of SAEs was comparable between treatment groups, and incidence of early termination due to AE was higher in the laquinimod 0.6 mg group. The safety signal of ALT elevation that was detected in the study population as a whole did not come up as a signal in the region of USA and Canada. This pattern of AEs corresponds to the relative incidence of shifts to PCS ALT levels.

Clinical Laboratory

Most subjects in both groups had normal values for most laboratory parameters at baseline. No laboratory parameter exhibited a distinct trend of elevation in mean group levels over time in the study.

In the laquinimod 0.6 mg group mean group levels of ALP, GGT and p-amylase were consistently higher than placebo and higher than baseline at all post-baseline visits.

Post-baseline shifts to abnormal biochemical values detected with a higher incidence in the

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laquinimod 0.6 mg group by at least 1% included shifts to abnormally high liver enzymes (ALT, AST and GGT), CPK, p-amylase, fibrinogen and potassium and shifts to abnormally low sodium.

Post-baseline shifts to PCS biochemical values detected with a higher incidence in the laquinimod 0.6 mg group by at least 1% were shifts to PCS high liver enzymes (ALT and GGT) and CRP.

Liver function tests: Laquinimod -treated subjects had a higher incidence of post-baseline shifts to ALT and AST levels >3xULN and ≤5xULN (3.5% vs. 0.5%). Incidence of shifts to levels >5xULN were similar or lower in the laquinimod 0.6 mg group compared to the placebo group. Subjects in both groups who reached ALT levels >8xULN (3 on laquinimod 0.6 mg and 4 on placebo) were immediately terminated from the study in accordance with pre-defined safety stopping rules. In all cases of laquinimod-treated subjects who reached PCS ALT levels (except for one subject whose PCS level was detected after last dose), ALT levels decreased to below PCS range: in 18 of 26 subjects (69%) without terminating from the study and in the remaining 8 subjects up to 2 months after last dose. For most laquinimod-treated subjects who reached levels>3xULN and <8xULN, (21 out of 23) elevations occurred once, within 6 months of first dose, and did not repeat after the decrease while still on drug.

All elevations of liver enzymes were asymptomatic. There were no cases of liver failure and no cases of liver insufficiency as evidenced by concomitant elevations of bilirubin or INR; no subject in the study met Hy's law. These elevations occurred with a higher incidence in male than in female laquinimod-treated subjects and were not observed in laquinimod-treated subjects located in the USA and Canada.

In the laquinimod 0.6 mg group, levels of white blood cells (WBC, neutrophils, lymphocytes and monocytes) were higher than placebo and higher than baseline at all visits. Levels of HgB, HCT and platelets were slightly lower than placebo and lower than baseline at all visits. In HgB and platelets there were slight trends of decrease in mean group levels over time in the study. Trough HgB mean group level was 12.9g/dL at Visit 9/ Month 21 (change from baseline: -0.5g/dL, -3.8%) and trough platelet mean group level was $234.2x10^9$/L at Visit 10/ Month 24 (change from baseline: $-18.7x10^9$/L, -7.3%).

Post-baseline shifts to abnormal hematological values detected with a higher incidence in the laquinimod 0.6 mg group by at least 1% were shifts to high white blood cells (WBC, neutrophils, lymphocytes and monocytes) and shifts to low hemoglobin (HgB, HCT and RBC) and platelets. Laboratory analyses did not suggest a laquinimod-related effect of leucopenia: post-baseline shifts to abnormally low white blood cells were reported with a lower incidence than placebo. A higher incidence in the laquinimod 0.6 mg group was also seen for subjects with 2 consecutive post-baseline abnormal values, for all of these parameters apart from monocytes.

Post-baseline shifts to PCS low HgB were reported with a higher incidence in the laquinimod 0.6 mg group. 11 subjects (2%, compared to 5 subjects, 0.9%) in the laquinimod 0.6 mg group had two or

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Laquinimod sodium	

more consecutive post-baseline PCS low HgB values. Review of individual data for these 11 subjects, revealed that all but one started the study with abnormally low HgB. There did not seem to be a pattern with respect to timing of decrease in HgB to PCS levels during treatment and none of the subjects had a sustained trend of decline in HgB. PCS low HgB levels were not accompanied by clinical manifestations and none of these subjects terminated study early due to low HgB levels.

Overall, the incidence of post baseline shifts to abnormal urinalysis findings was low. Of the subjects who had post-baseline shifts to abnormal findings, shifts reported with an incidence higher in the laquinimod 0.6mg by at least 1% were post-baseline shifts to abnormal urine blood and urine WBC.

Vital Signs and ECG:

Treatment groups were balanced with respect to BP and pulse values at baseline. Most subjects (at least 96%) in both groups had normal values for most vital signs at baseline.

No specific trend of change from baseline over time was seen for BP or pulse in either of the groups. In the laquinimod 0.6 mg group, post-baseline shifts to PCS low sitting systolic BP (SBP) were reported with a higher incidence in the laquinimod 0.6 mg group (11.7% vs. 10.3%). All other post baseline shifts to PCS values were reported with a low and similar incidence across treatment groups.

No subject was defined as having a baseline ECG abnormal, clinically significant or abnormal, clinical alert. This was in line with the protocol-specified exclusion criterion #18. There were no notable differences in mean values of any ECG parameter between treatment groups, at any time point during the study. No specific trend of change over time in any parameter was detected in any of the treatment groups. Incidence of shifts from a normal ECG at baseline to a clinically significant post-baseline ECG as assessed by the investigators was identical across treatment groups (3 subjects, 0.5% in each treatment group). Of the subjects who had a normal ECG at baseline, one laquinimod-treated subject (0.2%, compared to 2 subjects, 0.4% in the placebo group) had an abnormal, clinical alert post-baseline ECG as assessed by the eRT cardiologist. No laquinimod-treated subject had a QTc measurement of over 500msec at any time during the study. Treatment groups had a comparable incidence of subjects with changes in adjusted QTc from baseline that were longer than 60 msec (QTcB: 1.1% vs. 0.9% in the laquinimod 0.6 mg and placebo groups, respectively. QTcF: 0.2% in both groups). Changes from baseline that were longer than 60msec were mostly isolated events. No subject terminated the study due to abnormal ECG measurements.

Pregnancy:

Pregnancy was recorded in study MS-LAQ-301 for 14 subjects, 6 in the laquinimod 0.6 mg group and 8 in the placebo group. In the laquinimod 0.6 mg group, three subjects terminated study early due to pregnancy at a maximal gestational age of 12 weeks. Of those three, one subject terminated the study on gestational week 4 and gave birth to a normal male baby (weight: 3532 g); another subject ended the pregnancy by elective abortion following study termination and the third subject terminated the

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study on 12 weeks gestation age, had a risk of miscarriage for which she was hospitalized but carried the pregnancy to term and gave birth to a normal male baby (weight 2966 g). The three remaining pregnant subject completed the study according to protocol. One subject was pregnant one month prior to study entry, she ended the the pregnancy by elective abortion prior to first dose and serum pregnancy test taken at baseline was negative.The two other subjects temporarily stopped medication following positive pregnancy tests. The pregnancies were terminated by elective abortions. Following negative pregnancy tests the subject resumed and completed the study.

Overall Summary and Conclusion

The results obtained from this Phase III placebo-controlled study demonstrated a statistically significant treatment effect in favor of treatment with laquinimod 0.6 mg over placebo in the primary endpoint, the annualized relapse rate. Risk Ratio [95% CI] = 0.770 [0.650; 0.911], p-value=0.0024, reflecting a reduction of 23% in the risk for confirmed relapse based on the principal analysis model.

Statistically significant effect was demonstrated for three of the four secondary endpoints. The first two were MRI-based endpoints. The results for the cumulative number of T_1 Gd-enhancing lesions: Rate Ratio [95% CI] = 0.629 [0.488; 0.809], p-value=0.0003, reflect a reduction of 37% in the mean rate of developing T_1 Gd-enhancing lesions on laquinimod 0.6 mg compared to placebo. For the cumulative number of New/Enlarging T_2 lesions: Rate Ratio [95% CI] = 0.704 [0.584; 0.849], p-value=0.0002, a reduction of 30% in the the mean rate of developing New/Enlarging T_2 lesions on laquinimod 0.6 mg compared to placebo was demonstrated. The third secondary endpoint, time to first confirmed progression of EDSS, sustained for 3 months, showed a statistically significant treatment effect of laquinimod 0.6 mg over placebo: Hazard Ratio [95% CI] = 0.641 [0.452; 0.908], p-value=0.0122. This result demonstrates that laquinimod 0.6 mg reduced the risk for confirmed progression of EDSS by 36% compared to placebo, and delayed the time to disability. The fourth secondary endpoint, disability assessed by MSFC at Month 24 (termination/early discontinuation visit after Month 12), did not a show statistically significant difference between the treatment groups. It should be noted that the changes from baseline reflected by the Z-scores were of a very small magnitude in both group,s and especially in placebo, making it hard to detect differences between treatments

<u>Exploratory endpoints</u>

Among the exploratory endpoints, an effect of treatment with laquinimod 0.6 mg over placebo was shown for the relapse-related endpoints of time to first relapse, proportion of relapse-free subjects and rate of severe confirmed relapse.

For MRI-based endpoints, treatment with laquinimod 0.6 mg showed reduction in brain atrophy over placebo at Months 12 and 24, as well as benefit for treatment with laquinimod 0.6 mg over placebo in the cumulative number of new/enlarging hypointense lesions.

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No appreciable difference between laquinimod and placebo could be shown at Months 12 or 24 for the T_2 lesions volume or hypointense lesions volume, nor in visual acuity.

Treatment with laquinimod 0.6 mg was, on average, associated with less functional disability due to fatigue than for placebo treated subjects. General health status assessed by EQ-5D and SF-36 showed that the status of subjects treated with laquinimod 0.6 mg remained stable while that of placebo subjects declined.

Overall, treatment with laquinimod 0.6 mg demonstrated a benefit over placebo in decreasing the relapse rate, and in reducing the risk for EDSS progression. Reduction of the number of T_1 and New/Enlarging T_2 lesions, and brain atrophy were shown. Treatment with laquinimod 0.6 mg was, on average, associated with less functional disability due to fatigue than for placebo treated subjects. General health status assessed by EQ-5D and SF-36 showed that the status of subjects treated with laquinimod 0.6 mg remained stable while that of placebo subjects declined.

A thorough analysis of all safety data gathered in the MS-LAQ-301 (ALLEGRO) study identified a single safety signal of reversible, asymptomatic elevations in liver enzymes that did not result in liver failure and were not accompanied by elevations in bilirubin. No subject in the study met Hy's law. These elevations occurred with a higher incidence in male laquinimod-treated subjects and were not observed in laquinimod-treated subjects located in the USA and Canada.

Analysis of AEs as well as laboratory parameters did not reveal a signal suggestive of immunosuppression by laquinimod. Infections were reported with a similar incidence across treatment groups and no specific type of infecting organism was a safety signal of concern. Laboratory analyses did not suggest a laquinimod-related effect of leucopenia: post-baseline shifts to abnormally low white blood cells were reported with a lower incidence than placebo. Overall, malignant neoplasms were reported with similar incidence across treatment groups. Analysis of malignant neoplasms showed that all malignant neoplasms were reported by a single subject each in either group apart from SAEs included in the HLT malignant breast and nipple neoplasms that were reported for 3 subjects in the laquinimod 0.6 mg group and for 1 subject on placebo. One of the laquinimod-treated subjects had a medical history of ipsilateral breast cancer; bringing the total number of treatment-emergent AEs of this HLT to 2 on laquinimod and 1 on placebo. The number of malignant breast neoplasms is low, and does not allow drawing any conclusions about possible effects of the drug.

In the laquinimod 0.6 mg group, there was a slight trend of decrease in mean group levels of HgB and platelets (trough levels representing a decrease by 3.8% and 7.3%, respectively) that was not detected in the placebo group. Post baseline shifts to PCS low HgB levels were reported with a higher incidence in the laquinimod 0.6 mg group. Review of individual data for subjects with two or more

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consecutive post-baseline PCS low HgB values, revealed that all but one started the study with abnormally low HgB. There did not seem to be a pattern with respect to timing of decrease in HgB to PCS levels during treatment and none of the subjects had a sustained trend of decline in HgB. PCS low HgB levels were not accompanied by clinical symptoms and none of these subjects terminated the study early due to low HgB levels.

None of the AEs previously identified as safety signals of laquinimod's predecessor compound, linomide: pancreatitis, pericarditis, pleuritis, arthritis and ischaemic coronary artery disorders came up in the ALLEGRO study as a safety signal for laquinimod.

There was no evidence for laquinimod-related effects on ECG, vital signs or weight. No pregnancy of a laquinimod-treated subject resulted in fetal abnormalities or spontaneous miscarriage; the two laquinimod-treated subjects who carried their pregnancies to term after withdrawal from the study gave birth to healthy babies.

Together, efficacy and safety results of the ALLEGRO study support a favorable benefit-to-risk ssessment for the laquinimod 0.6 mg dose in the treatment of patients with RRMS.