## 2 SYNOPSIS

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| **Name of Sponsor/Company**:<br>Teva Pharmaceutical Industries, Ltd.,<br>POB 8077,<br>Sapir Industrial Zone, Kiryat Nordau,<br>Netanya 42504,<br>Israel<br>**Code Name of Finished Product:**<br>TV-5600 (previously ABR-215062)<br>**Name of Active Ingredients:**<br>Laquinimod sodium | **Protocol No.: MS-LAQ-302** |

**Study Title**

A multinational, multicenter, randomized, parallel-group study performed in subjects with relapsing-remitting multiple sclerosis (RRMS) to assess the efficacy, safety and tolerability of laquinimod over placebo in a double-blind design and of a reference arm of interferon β-1a (Avonex®) in a rater-blinded design.

**Study Principal Investigators**

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**Study Site Investigators and Respective Study Sites**

155 sites, with their respective 155 site investigators participated in the study. Details for all sites and investigators are presented in the clinical study report.

**Publication Based on Study Results**

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| **Study Dates**<br>First patient in: April 24, 2008<br>Last Patient out: June 10, 2011 | **Clinical Phase** III |

**Test Drug, Dose and Mode of Administration, Batch Number**

Laquinimod sodium, 0.6 mg, oral. Batch number: K-38300 K-41962

**Reference Drug, Dose and Mode of Administration, Batch Number**

Matching placebo. Batch number: K-38303 K-41992

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| Interferon β-1a (Avonex®), 30 mcg, intramuscular injection. Batch number: 080021A, 080118A, 080247A, 080458A, 090068A, 090167A and 100100A | |

**Objectives**

To assess the efficacy, safety and tolerability of laquinimod over placebo in a double-blind design and of a reference arm of interferon β-1a (Avonex®), in a rater-blinded design and to perform a comparative benefit/risk assessment between oral laquinimod and injectable Avonex®.

The primary objective was to assess the efficacy of 0.6 mg daily dose of laquinimod in subjects with RRMS, as measured by the number of confirmed relapses during the treatment period.

The secondary objectives were:

- To assess the effect of 0.6 mg daily dose of laquinimod on the development of brain atrophy as defined by the percent brain volume change from baseline at the end of the treatment period.
- To assess the effect of 0.6 mg daily dose of laquinimod on the accumulation of physical disability as measured by the time to confirmed progression of the Kurtzke's expanded disability status scale (EDSS) during the treatment period. (A confirmed progression of EDSS is defined as a 1 point increase from baseline on EDSS score if baseline EDSS was between 0 and 5.0, or a 0.5 point increase if baseline EDSS was 5.5, confirmed 3 months later. Progression cannot be confirmed during a relapse).
- To assess the effect of 0.6 mg daily dose of laquinimod on the accumulation of disability, as assessed by the multiple sclerosis functional composite (MSFC) score at the end of the treatment period.

**Methodology**

This was a multinational, multicenter, randomized, double-blind, parallel-group study performed in subjects with RRMS to assess the efficacy, safety and tolerability of laquinimod 0.6 mg over placebo and of a reference arm of interferon β-1a (Avonex®) in a rater-blinded design.

Eligible subjects were randomized in a 1:1:1 ratio (oral laquinimod: oral placebo: Avonex®) and assigned to one of the following three treatment arms:

Laquinimod 0.6 mg per os (PO) once daily

Matching placebo (for laquinimod) PO once daily

Interferon β-1a (Avonex®) 30 mcg intramuscular (IM) injection once weekly.

During the treatment phase, subjects were evaluated at study sites for a total of 12 scheduled visits at months: -1 (screening), 0 (baseline), 1, 2, 3, 6, 9, 12, 15, 18, 21 and 24 (termination/early discontinuation).

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Subjects on oral treatment were managed in a double-blind manner. Subjects assigned to injectable treatment with Avonex® and their Treating Neurologist/ Physician were unblinded to the treatment assignment, but assessed neurologically by an Examining Neurologist/Physician in a blinded manner (potential IM injection sites were covered).

**Number of Subjects (total and for each treatment):** 1331 subjects; 434 on laquinimod 0.6 mg, 450 on matching placebo and 447 on Avonex®.

**Diagnosis and Main Criteria for Inclusion**

**Inclusion:**

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

- Subjects must have a confirmed and documented MS diagnosis as defined by the Revised McDonald criteria [Ann Neurol 2005: 58:840-846], with a relapsing-remitting disease course.
- Subjects must have been ambulatory with converted EDSS score of 0-5.5 in both screening and baseline visits.
- Subjects must be in a stable neurological condition and free of corticosteroid treatment [intravenous (IV), IM and/or PO] 30 days prior to screening (Month -1) and between screening (Month -1) and baseline (Month 0) visits.
- 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 T1 gadolinium (Gd)-enhancing lesion in a magnetic resonance imaging (MRI) scan performed within 12 months prior to screening.
- Subjects had to be between 18 and 55 years of age, inclusive.
- Women of child-bearing potential must practice an acceptable method of birth control [acceptable methods of birth control in this study include: surgical sterilization, intrauterine devices, oral contraceptive, contraceptive patch, long-acting injectable contraceptive, partner's vasectomy or a double-barrier method (condom or diaphragm with spermicide)].
- Subjects had to be able to sign and date a written informed consent prior to entering the study.
- Subjects had to be willing and able to comply with the protocol requirements for the duration of the study.

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**Exclusion:**

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

- An onset of relapse or any treatment with corticosteroids (IV, IM and/or per os [PO]) or adrenocorticotropic hormone (ACTH) between month -1 (screening) and 0 (baseline).
- Subjects with progressive forms of MS.
- Use of experimental or investigational drugs, and/or participation in drug clinical studies within the 6 months prior to screening.
- Use of immunosuppressive (including mitoxantrone (Novantrone®) or cytotoxic agents within 6 months prior to screening.
- Previous use of either of the following: natalizumab (Tysabri®), cladribine, laquinimod, interferon beta-1a (Avonex® or Rebif®), interferon beta-1b (Betaseron®/Betaferon®) or any other experimental interferon-beta for MS.
- Previous treatment with glatiramer acetate (Copaxone®) or IV immunoglobulin (IVIG) within 2 months prior to screening visit.
- Chronic (more than 30 consecutive days) systemic (IV, PO or IM) corticosteroid treatment within 2 months prior to screening visit.
- Previous total body irradiation or total lymphoid irradiation.
- Previous stem cell treatment, autologous bone marrow transplantation or allogenic bone marrow transplantation.
- A known history of tuberculosis.
- Acute infection within 2 weeks prior to baseline visit.
- Major trauma or surgery within 2 weeks prior to baseline visit.
- Known human immunodeficiency virus (HIV) positive status.
- Use of inhibitors of CYP3A4 (cytochrome P) within 2 weeks prior to baseline visit.
- Use of amiodarone within 2 years prior to screening visit.
- Pregnancy or breastfeeding.
- A serum elevation ≥3x upper limit of normal (ULN) of either alanine aminotransferase (ALT) or aspartate aminotransferase (AST) at screening.
- Serum direct bilirubin which is ≥2x ULN at screening.

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- A QTc interval which is ≥450 msec (according to machine output), obtained from:
  - Two electrocardiogram (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 examinations, ECG, laboratory tests or chest X-ray. Such conditions may include:
  - A cardiovascular or pulmonary disorder that cannot be well-controlled by standard treatment permitted by the study protocol.
  - A gastrointestinal disorder that may affect the absorption of study medication.
  - Renal, metabolic or hematological diseases.
  - Thyroid disease: A subject with hyperthyroidism is not permitted to participate in the study. A subject with hypothyroidism may be permitted to participate in the study provided that he/she is clinically euthyroid and considered stable.
  - Liver disease, such as cirrhosis.
  - A family history of long-QT syndrome.
  - A history of drug and/or alcohol abuse.
  - A current major psychiatric disorder, including schizophrenia or severe depression, with or without suicidal ideation.
  - A history of seizure disorder, with the last convulsion occurring within 12 months prior to screening visit.
- A known history of sensitivity to Gd.
- Inability to successfully undergo MRI scanning.
- A known drug hypersensitivity that would preclude administration of laquinimod, such as hypersensitivity to: mannitol, meglumine or sodium stearyl fumarate.
- A known history of hypersensitivity to natural or recombinant interferon β-1a, human albumin, or any other component of the formulation of Avonex®.

**Duration of Treatment**

- Screening phase: 1 month
- Treatment phase: 24 months of once-daily oral administration of laquinimod 0.6 mg, matching

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oral placebo or once-weekly intramuscular administration of interferon β-1a (Avonex®) 30 mcg

Subjects successfully completing the study were offered the opportunity to enter an open-label extension phase (MS-LAQ-302E) in which laquinimod 0.6 mg/day would be administered until 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 number of confirmed relapses during the treatment period.

Secondary Endpoints:

- Brain atrophy as defined by the percent change from baseline in normalized brain volume at Month 24 (termination/early discontinuation visit if occurred after Month 12)
- Accumulation of physical disability measured by the time to confirmed progression of EDSS during the treatment period (A confirmed progression of EDSS is defined as a 1 point increase from baseline on EDSS score if baseline EDSS was between 0 and 5.0, or a 0.5 point increase if baseline EDSS was 5.5, confirmed 3 months later. Progression can not be confirmed during a relapse).
- Disability as assessed by the MSFC score at Month 24 (termination/early discontinuation visit after Month 12).

Exploratory Endpoints:

- The cumulative number of enhancing lesions on $T_1$-weighted images taken at Months 12 and 24 (termination/early discontinuation visit after month 12)
- The number of enhancing lesions on a $T_1$-weighted image taken at Month 12
- The number of enhancing lesions on a $T_1$-weighted image taken at Month 24 (termination/early discontinuation visit after Month 12)
- The cumulative number of new or enlarging hypointense lesions on enhanced $T_1$ scans taken at Months 12 and 24 (termination/early discontinuation after Month 12)
- The number of new or enlarging hypointense lesions on an enhanced $T_1$ scan taken at Month 12
- The number of new or enlarging hypointense lesions on an enhanced $T_1$ scan taken at Month 24 (termination/early discontinuation visit after Month 12) [Note: analysis was not performed as data for Month 24 relative to baseline were not obtained]
- The cumulative number of new or enlarging $T_2$ lesions on scans taken at Months 12 and 24

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(termination/early discontinuation visit after month 12)

- The number of new or enlarging $T_2$ lesions on a scan taken at Month 12
- The number of new or enlarging $T_2$ lesions on a scan taken at Month 24 (termination/early discontinuation visit after month 12) [Note: Analysis was not performed as data for Month 24 relative to baseline were not obtained]
- The volume of $T_2$ lesions at Month 24 (termination /early discontinuation visit after month 12)
- The volume of $T_2$ lesions at Month 12
- The volume of hypointense lesions on enhanced $T_1$ scans at Month 24 (termination/early discontinuation visit after Month 12)
- The volume of hypointense lesions on enhanced $T_1$ scans at Month 12
- Brain atrophy as defined by the percent brain volume change from (a) baseline to Month 12, and (b) Month 12 to Month 24 (termination/early discontinuation after Month 12)
- Subject-reported fatigue, as assessed by the Modified Fatigue Impact Scale (MFIS) change from baseline to Month 24 (termination/early discontinuation visit after Month 12)
- The time to the first confirmed relapse during the study period
- The proportion of relapse-free subjects
- The rate of confirmed relapses during the study period requiring hospitalization and/or IV steroids
- The change from baseline to Month 24 (termination/early discontinuation visit after Month 12) in general health status as assessed by the EuroQoL (EQ-5D) questionnaire
- The change from baseline to Month 24 (termination/early discontinuation visit after Month 12) in general health status and health-related quality of life, as assessed by the Short-Form general health survey (SF-36) subject-reported questionnaire for physical and mental domains
- The change from baseline to Month 24 (termination/early discontinuation visit) in binocular visual acuity, as assessed by the number of letters read correctly from 2 meters distance on 1.25%, 2.5% and 100% contrast Sloan letter/Tumbling E charts.

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**Statistical Methods**

**Data analysis sets:**

- Intent-To-Treat analysis set (ITT): Consisted of all subjects who were randomized. In accordance with the ITT principle, all subjects randomized were kept in their originally assigned treatment group. This analysis set served as the principal analysis set for the primary analysis inference.
- Completers analysis set (CO): Consisted of all subjects who completed the 24 months of double-blind treatment.
- Evaluable analysis set (EV): This was a subset of the CO analysis set. It consisted of all subjects in the CO analysis set who complied with major protocol guidelines, including: meeting study's key inclusion and exclusion criteria, not using disallowed medications, and keeping the laquinimod dosing regimen.
- Safety analysis set (ST): Consisted of all subjects who were randomized and received at least one dose of laquinimod.

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, 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 employing the hierarchical approach (i.e. each secondary endpoint was analyzed only in case the preceding endpoint had a p-value less or equal to 0.05 for laquinimod 0.6 mg over placebo comparison).

Primary Endpoint

The principal statistical analysis of the annualized relapse rate during study was performed on the ITT analysis set and was based on the outcome of a contrast (laquinimod 0.6 mg vs placebo) derived from a baseline-adjusted, negative binomial regression (SAS® PROC GENMOD with DIST=NB). Subject's number of relapses during the double-blind, placebo-controlled phase served as the response variable. Within the same model an additional exploratory contrast was constructed to assess the treatment effect of Avonex® vs placebo.

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 following covariates: baseline EDSS score, log of (prior 2-year number of relapses+1) and country or geographical region (CGR).

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A *post hoc* exploratory comparison of laquinimod 0.6mg to Avonex® employed the same model.

The robustness of the results obtained by the principal analysis was explored by applying the principal model (negative binomial) to the CO and EV analysis sets. Additional models were applied to the ITT analysis set as follows: negative binomial without covariates, over-dispersed Poisson regression (with and without covariates), Analysis of Covariance (ANCOVA; with and without covariates) and the Wilcoxon rank-sum test. A sensitivity analysis to missing values was also conducted to estimate the amount of treatment effect preserved in Missing Not At Random (MNAR) pattern of missingness.

Secondary Endpoints

Analysis of brain atrophy, as defined by the percent volume change from baseline to termination/early discontinuation visit after Month 12, was based on the outcome of a contrast (laquinimod 0.6 mg vs placebo) derived from a baseline-adjusted ANCOVA (SAS® PROC GLM). In addition to treatment group, the model also included as covariates the number of enhancing lesions on T1-weighted images taken at baseline and CGR. Within the same model an additional exploratory contrast was constructed to assess the treatment effect of Avonex® vs placebo.

The second endpoint, time to EDSS progression confirmed after 3 months, was analyzed based on Cox's Proportional Hazard (PH) model (SAS® PROC PHREG). The model also included the baseline EDSS score, the log of the (prior 2-year number of relapses +1) and CGR as covariates. The time to confirmed progression of EDSS was also presented by Kaplan-Meier curves stratified by treatment group. Within the Cox PH model, an additional exploratory contrast was constructed to assess the treatment effect of Avonex® vs placebo.

The third endpoint, disability as assessed by the MSFC score at Month 24 (termination/early discontinuation visit after Month 12), was analyzed based on the outcome of a contrast (laquinimod 0.6 mg vs placebo) derived from a baseline-adjusted ANCOVA (SAS® PROC GLM), with baseline MSFC, baseline EDSS, log of the (prior 2-year number of relapses +1) and CGR as covariates. Within the same model an additional exploratory contrast was constructed to assess the treatment effect of Avonex® vs placebo.

**Summary of Results**

Subject Disposition:

A total of 1,331 subjects were randomized into the study: 434 subjects to laquinimod 0.6 mg, 450 subjects to placebo and 447 subjects to Avonex® (reference arm). A total of 241 subjects (18.1%) prematurely terminated the study with a similar incidence for the laquinimod 0.6 mg and placebo groups and a lower incidence for the Avonex® group (18.7%, 20.2% and 15.4% respectively). Subjects who terminated the study prematurely were invited to a follow-up visit one month later.

The most common reasons for early termination from the study were consent withdrawal (8.5%,

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8.7% and 6.0%, for laquinimod 0.6 mg, placebo and Avonex®, respectively) and adverse event (AEs) (4.8%, 4.2% and 5.8%, for laquinimod 0.6 mg, placebo and Avonex®, respectively). Mean time (± standard deviation [SD]) since first symptom was 6.6 (±6.0), 6.9 (±6.6) and 7.0 (±5.9) years on laquinimod 0.6 mg, placebo and Avonex®, respectively. The mean (±SD) number of exacerbations in the 2-years prior to screening was 1.9 (±0.9) years for placebo and Avonex® subjects, and 1.9 (±1.0) for laquinimod 0.6 mg subjects. Mean (±SD) baseline converted EDSS score was 2.7 (±1.3) for laquinimod 0.6 mg, 2.7 (±1.2) for placebo and 2.6 (±1.2) for Avonex®.

A higher proportion of subjects had one or more T1 Gd-enhancing lesions at baseline in the laquinimod (39.6%) and Avonex® (38.1%) treatment groups compared to the placebo group (33.4%). T2 lesions volume also differed between the three groups at baseline: mean (±SD) values ($cm^3$) were 9.6 (±10.3) for laquinimod 0.6 mg, 8.6 (±10.4) for Avonex® and 7.9 (±8.9) for placebo.

**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, did not demonstrate a statistically significant treatment effect of laquinimod 0.6 mg over placebo: the risk ratio [95% CI] was 0.823 [0.664; 1.020], reflecting a 17.7% reduction in the annualized relapse rate (p-value=0.0746). Comparison of the Avonex® reference arm with placebo yielded a risk ratio [95% CI] of 0.741 [0.596; 0.920], reflecting a reduction of 25.9% in the annualized relapse rate on Avonex® (p-value=0.0067).

The observed treatment effect, as well as the placebo annualized relapse rate (ARR) led to *post hoc* assessment of the study power. The predefined sample size calculation for the BRAVO study employed (among others) the following two assumptions:

- In the placebo treatment group, the expected annualized relapse rate is 0.6 relapses per year.
- Treatment with laquinimod will reduce the subject population's ARR by 25% or more when compared to the placebo group. That is, the expected ARR of the laquinimod treated population is 0.45 relapses per year or less.

Results of the BRAVO study disproved both assumptions: the observed relapse rate in the placebo group (0.344 relapse a year) was much lower than anticipated and the effect of laquinimod 0.6 mg/day (17.7% reduction) was lower than anticipated. *Post-hoc* power calculations revealed that under the observed assumptions and dropout rate the actual power of BRAVO was only 42%. Hence, the study was underpowered to detect the treatment effect and this may partially account for the p-value higher than 5%.

*Post-hoc* review of the baseline characteristics of the study population revealed differences between the treatment groups in the baseline mean $T_2$ lesions volume and percent of subjects with $T_1$ Gd-enhancing lesions. These two MRI parameters, when introduced to the primary model, were

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found to be strong predictors of the rate of relapses during the double-blind treatment phase (β linear estimates of 0.45 with p-value<0.0001 and 0.0112 with p-value=0.0126 for the categorical Gd-enhancing $T_1$ lesions and continuous $T_2$ volume variables, respectively).

Inclusion of these two additional covariates (baseline $T_2$ lesions volume as a continous variable and an indicator variable for the presence or absence of $T_1$ Gd-enhancing lesions at baseline) into the primary analysis model as a sensitivity analysis increased the reduction in ARR vs placebo to 21.3% (p=0.0264) for laquinimod 0.6 mg and to 28.6% (p=0.0021) for Avonex®.

Sensitivity analyses using other distributional assumptions for the number of relapses (over-dispersed Poisson, ANCOVA or Wilcoxon) with and without additional baseline MRI covariates did not alter the results appreciably from the primary analysis assumption of negative binomial distribution. Also, sensitivity analysis for missing data patterns revealed that the overall findings are robust to the amount of treatment effect preserved in the MNAR missingness data.

An additional *post-hoc* sensitivity analysis is introduced herein employing a propensity score approach. The propensity score (D'Agostino, 1998) is a useful tool to summarize, simultaneously, potential bias concealed in many baseline covariates in a single number. The propensity score overcomes the limitations imposed by one's decision to include certain covariates over others. The results of this analysis (see Appendix 16.1.9.1.1) demonstrated that indeed an unexpected bias was introduced in the original pre-planned analysis due to imbalance in important baseline characteristics and hence supports the sensitivity analysis which included additional covariates and was introduced above.

A *post-hoc* exploratory comparison of the ARR of laquinimod 0.6mg and Avonex® yielded a Risk Ratio of 1.102 with p=0.3887 (95%CI – 0.883-1.376) suggesting that under the BRAVO design, the apparent superiority of Avonex® over laquinimod was rejected. Further, the difference in ARR reduction (as compared to placebo) between laquinimod 0.6mg and Avonex® was 0.03 relapses a year, and it is the Sposor's assessment that it is not clinically meaningful.

Secondary Endpoints:

According to the hierarchical approach, since the primary endpoint did not achieve statistical significance, inferential testing of the secondary endpoints does not ensure preservation of the overall type-I error and hence the results should be interpreted in an exploratory manner.

For each secondary endpoint, *post-hoc* analysis was performed using the original model (as described above), with correction for the two additional MRI covariates (baseline $T_2$ lesions volume and indicator for subjects with number of $T_1$ Gd-enhancing lesions ≥1 at baseline), as used in the primary endpoint sensitivity analysis described above.

Results are summarized in **TABLE 1**.

The first secondary endpoint, brain atrophy as defined by the percent change in brain volume from

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baseline, was analyzed using baseline-adjusted ANCOVA. The results showed a 27.6% reduction in brain atrophy on laquinimod 0.6 mg versus placebo (p=0.0001) at Month 24 (or termination/early discontinuation visit after Month 12). Results obtained from the *post-hoc* analysis corrected for the two additional MRI parameters (baseline T2 lesions volume and indicator for subjects with T1 Gd-enhancing lesions ≥1 at baseline) were similar to those of the original analysis.

For the Avonex® vs placebo treatment comparison, no appreciable difference in brain atrophy at Month 24 (termination/early discontinuation visit after Month 12) could be demonstrated, either with the original analysis or the *post-hoc* analysis corrected for the baseline MRI imbalance.

The two clinical secondary endpoints were time to confirmed progression of EDSS sustained for 3 months during the double-blind treatment period, analyzed using Cox's proportional hazards model, and disability as assessed by MSFC at Month 24 (or termination/early discontinuation visit after Month 12), analyzed using baseline-adjusted ANCOVA. Both of these endpoints, showed a reduction in the laquinimod 0.6 mg group compared to placebo (EDSS progression reduction by 31.3% with p=0.0628; and MSFC z-score reduction by 77.0% with p-value=0.1505). *Post-hoc* analysis incorporating the two additional MRI covariates into the model revealed a treatment effect in favor of laquinimod 0.6 mg over placebo in EDSS progression (33.5% reduction with p=0.0440). Results obtained in the *post-hoc* analysis for MSFC z-score were similar to those obtained with the original analysis.

Comparison between Avonex® treatment and placebo showed a reduction by 25.8% in EDSS progression (p=0.1269) and 65.9% reduction in MSFC z-score (p=0.2083). Results obtained for both secondary endpoints following post-hoc analyses incorporating the two additional MRI covariates were similar to those obtained with the original analysis.

**TABLE 1: Secondary Endpoints**

| **Analysis Results** | **Laquinimod 0.6 mg vs Placebo** | | **Avonex® vs Placebo** | |
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| | **Original Analysis** | **Corrected Analysis*** | **Original Analysis** | **Corrected Analysis*** |
| **Brain Atrophy at Month 24 (Termination/Early Discontinuation Visit After Month 12)** | | | | |
| **Adjusted Mean Difference [95% CI]** | **0.284 [0.139; 0.429]** Reflecting a 27.6% reduction | **0.313 [0.168; 0.459]** Reflecting a 27.5% reduction | **-0.107 [-0.249; 0.035]** Reflecting a 10.4% increase | **-0.108 [-0.250; 0.035]** Reflecting a 9.5% increase |
| **P-Value** | **0.0001** | **<0.0001** | **0.1392** | **0.1380** |
| **Time to Confirmed Progression of EDSS** | | | | |
| **Hazard Ratio [95% CI]** | **0.687 [0.462; 1.020]** Reflecting a 31.3% reduction | **0.665 [0.447; 0.989]** Reflecting a 33.5% reduction | **0.742 [0.507; 1.088]** Reflecting a 25.8% reduction | **0.713 [0.484; 1.051]** Reflecting a 28.7% reduction |
| **P-Value** | **0.0628** | **0.0440** | **0.1269** | **0.0878** |

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| **Disability as Assessed by MSFC** | | | | |
|---|---|---|---|---|
| **Adjusted Mean Difference [95% CI]** | **0.104 [-0.038; 0.247]** Reflecting a 77.0% reduction | **0.115 [-0.028; 0.258]** Reflecting a 77.2% reduction | **0.089 [-0.050; 0.229]** Reflecting a 65.9% reduction | **0.095 [-0.045; 0.235]** Reflecting a 63.8% reduction |
| **P-Value** | **0.1505** | **0.1152** | **0.2083** | **0.1852** |

* Analysis was performed *post-hoc* using original model corrected for the two additional MRI covariates (T2 lesions volume and indicator for subjects with number of T1 Gd-enhancing lesions ≥1 at baseline)

Exploratory *post hoc* comparisons of laquinimod and Avonex treatment effects were performed on all secondary endpoints. In the first secondary endpoint, brain atrophy, the laquinimod 0.6 mg treatment effect was larger than that of Avonex® showing a reduction of 27.6% compared to placebo whereas Avonex® showed no appreciable effect. For the clinical endpoint of EDSS progression, the treatment effects of laquinimod 0.6 mg and Avonex® were comparable (31.3% and 25.8% for laquinimod 0.6 mg and Avonex®, respectively). Direct comparison of effects on EDSS progression yielded a hazard ratio of 0.931with p=0.7399. The effect of laquinimod 0.6mg and Avonex® on MSFC z-score was comparable (77% and 65.9% for laquinimod 0.6 mg and Avonex®, respectively). A direct comparison of laquinimod and Avonex® treatment effects on MSFC z-score yielded adjusted means difference of 0.020 with p=0.7810.

Exploratory Endpoints:

For relapse-related exploratory endpoints (see **TABLE 2**), improvements were observed for laquinimod 0.6 mg compared to placebo for time to first confirmed relapse, proportion of relapse-free subjects and rate of severe relapses requiring hospitalization and/or administration of steroids. A benefit for Avonex® over placebo was observed more definitively for all three relapse-related endpoints.

**TABLE 2: Relapse-Related Exploratory Endpoints**

| **Analysis Results** | **Laquinimod 0.6 mg vs Placebo** | **Avonex® vs Placebo** |
|---|---|---|
| **Time to First Confirmed Relapse During the Treatment Period** | | |
| Hazard Ratio [95% CI] | 0.835 [0.670; 1.040] | 0.741 [0.593; 0.927] |
| P-Value | 0.0875* | 0.0087 |
| **Proportion of Relapse-Free Subjects** | | |
| Odds Ratio [95% CI] | 1.198 [0.904; 1.587] | 1.388 [1.046; 1.842] |
| P-Value | 0.2089 | 0.0233 |
| **Rate of Confirmed Relapses Requiring Hospitalization and/or IV Steroids** | | |
| Risk Ratio [95% CI] | 0.835 [0.668; 1.045] | 0.744 [0.593; 0.934] |
| P-Value | 0.1152 | 0.0106 |

*p-value was taken from log rank test as proportional hazards assumption was not met

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Results for MRI-related exploratory endpoints are summarized in **TABLE 3**.

- **$T_1$ lesions:** A favorable effect of laquinimod 0.6 mg over placebo was observed for reduction of $T_1$ lesions at Month 24 but not at Month 12; there was a trend towards a reduction in the cumulative lesions count for Months 12 and 24. Treatment with Avonex® showed a reduction versus placebo in the number of $T_1$ lesions at both Month 12 and Month 24 measurements, as well as for the cumulative lesion count for Months 12 and 24.
- **$T_2$ lesions:** A favorable effect of laquinimod 0.6 mg versus placebo was seen for reduction of new $T_2$ lesions at Month 12; there was a mild difference between the two groups in favor of laquinimod 0.6 mg for the cumulative new T2 lesions count for Months 12 and 24. Treatment with Avonex® showed an appreciable reduction versus placebo for both endpoints. No appreciable differences between laquinimod 0.6 mg and placebo were observed for $T_2$ lesions volume, either at Month 12 or Month 24. A favorable effect for Avonex® over placebo was seen for both endpoints.
- **$T_1$ hypointense lesions:** No appreciable difference between laquinimod 0.6 mg and placebo was shown for the number of new/enlarging hypointense lesions, either at Month 12 or for the cumulative hypointense lesion count for Months 12 and 24. For Avonex® there was an appreciable reduction vs placebo for both endpoints. No differences between laquinimod 0.6 mg and placebo were observed for $T_1$ hypointense lesions volume, either at Month 12 or Month 24; there was no difference between the Avonex® and placebo groups for either endpoint.
- **Brain atrophy:** Laquinimod 0.6 mg demonstrated an appreciable reduction in brain atrophy over placebo from baseline to Month 12, whereas no appreciable difference between the two groups was shown between Months 12 to 24; no treatment effects on reduction in brain atrophy were seen for Avonex® over placebo for either measurement period.

No appreciable differences between laquinimod 0.6 mg and placebo were observed for change from baseline to Month 24 in any of the following exploratory endpoints related to health status and quality of life (see **TABLE 4**): subject-reported fatigue (assessed by MFIS score); any of the EQ-5D dimensions or subjects' subjective overall health assessment scores (EQ-5D-VAS); general health status assessed by SF-36 (both physical and mental component summary scores); and binocular visual acuity. Similarly, no appreciable differences could be demonstrated between Avonex® and placebo for these endpoints, with the exception of subjects' subjective overall health assessment scores, for which there was a lesser decline from baseline in health status at Month 24 for subjects on Avonex® compared to those on placebo.

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**TABLE 3: MRI-Based Exploratory Endpoints**

| Analysis Results | Laquinimod 0.6 mg vs Placebo | Avonex® vs Placebo |
|---|---|---|
| **Cumulative No. of Enhancing Lesions on T1-Weighted Images at M12 and M24*** | | |
| Rate Ratio [95% CI] | 0.785 [0.604; 1.019] | 0.385 [0.293; 0.505] |
| P-Value | 0.0691 | <0.0001 |
| **No. of Enhancing Lesions on T1-Weighted Images Taken at M12** | | |
| Rate Ratio [95% CI] | 0.884 [0.659; 1.186] | 0.410 [0.299; 0.562] |
| P-Value | 0.4099 | <0.0001 |
| **No. of Enhancing Lesions on T1-Weighted Images Taken at M24*** | | |
| Rate Ratio [95% CI] | 0.611 [0.439; 0.852] | 0.336 [0.237; 0.474] |
| P-Value | 0.0037 | <0.0001 |
| **Cumulative No. of New/Newly Enlarging T2 Lesions on Scans at M12 and M24*** | | |
| Rate Ratio [95% CI] | 0.835 [0.683; 1.021] | 0.489 [0.400; 0.597] |
| P-Value | 0.0782 | <0.0001 |
| **Number of New/Newly Enlarging T2 Lesions on Scans at M12** | | |
| Rate Ratio [95% CI] | 0.813 [0.664; 0.996] | 0.491 [0.400; 0.602] |
| P-Value | 0.0462 | <0.0001 |
| **Cumulative No. of New/Enlarging Hypointense Lesions on Enhanced T1 Scans at M12 and M24*** | | |
| Rate Ratio [95% CI] | 0.973 [0.822; 1.153] | 0.786 [0.664; 0.929] |
| P-Value | 0.7556 | 0.0049 |
| **No. of New/Enlarging Hypointense Lesions on Enhanced T1 Scans at M12** | | |
| Rate Ratio [95% CI] | 0.959 [0.793; 1.159] | 0.822 [0.681; 0.992] |
| P-Value | 0.6646 | 0.0411 |
| **Volume of T2 Lesions at M24*** | | |
| Geometric Means Ratio [95% CI] | 1.005 [0.930; 1.085] | 0.906 [0.839; 0.977] |
| P-Value | 0.9019 | 0.0104 |
| **Volume of T2 Lesions at M12** | | |
| Geometric Means Ratio [95% CI] | 0.996 [0.925; 1.071] | 0.892 [0.830; 0.959] |
| P-Value | 0.9053 | 0.0019 |
| **Volume of Hypointense Lesions on Enhanced T1 scans at M24*** | | |
| Geometric Means Ratio [95% CI] | 1.003 [0.939; 1.073] | 0.970 [0.908; 1.036] |
| P-Value | 0.9206 | 0.3659 |
| **Volume of Hypointense Lesions on Enhanced T1 Scans at M12** | | |
| Geometric Means Ratio [95% CI] | 0.987 [0.930; 1.048] | 0.969 [0.914; 1.028] |
| P-Value | 0.6711 | 0.2981 |
| **Brain Atrophy (a): Percent Brain Volume Change from Baseline to M12** | | |
| Adjusted Mean Diff. [95% CI] | 0.221 [0.125; 0.317] | -0.134 [-0.229; -0.040] |
| P-Value | <0.0001 | 0.0053 |
| **Brain Atrophy (b): Percent Brain Volume Change from M12 to M24*** | | |
| Adjusted Mean Diff. [95% CI] | 0.033 [-0.062; 0.127] | 0.018 [-0.074; 0.111] |
| P-Value | 0.4972 | 0.6975 |

*Or termination/early discontinuation visit after Month 12

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**TABLE 4: Exploratory Endpoints Related to General Health Status and Quality of Life**

| **Analysis Results** | | **Laquinimod 0.6 mg vs Placebo** | **Avonex® vs Placebo** |
|---|---|---|---|
| **Subject-Reported Fatigue – MFIS Change from Baseline to M24*** | | | |
| Adjusted Mean Diff. [95% CI] | | -0.274 [-2.217; 1.668] | -0.671 [-2.569; 1.226] |
| P-Value | | 0.7817 | 0.4877 |
| **General Health Status Change from Baseline to M24* – EQ-5D Questionnaire (Individual EQ-5D Dimensions)** | | | |
| **Mobility** | Odds Ratio [95% CI] | 1.072 [0.733; 1.566] | 1.013 [0.699; 1.466] |
| | P-Value | 0.7209 | 0.9473 |
| **Self-Care** | Odds Ratio [95% CI] | 1.265 [0.832; 1.923] | 0.967 [0.649; 1.441] |
| | P-Value | 0.2711 | 0.8698 |
| **Usual Activities** | Odds Ratio [95% CI] | 1.138 [0.813; 1.591] | 1.055[0.760; 1.463] |
| | P-Value | 0.4518 | 0.7500 |
| **Pain/Discomfort** | Odds Ratio [95% CI] | 1.324 [0.957; 1.833] | 1.158 [0.844; 1.590] |
| | P-Value | 0.0903 | 0.3628 |
| **Anxiety/Depression** | Odds Ratio [95% CI] | 1.153 [0.844; 1.576] | 1.117 [0.823; 1.516] |
| | P-Value | 0.3713 | 0.4761 |
| **General Health Status Change from Baseline to M24* – EQ5D Questionnaire (Overall Subjective Health Status Assessment, EQ-5D-VAS)** | | | |
| Adjusted Mean Diff. [95% CI] | | -1.311 [-3.732; 1.109] | -2.514 [-4.904; -0.123] |
| P-Value | | 0.2881 | 0.0393 |
| **General Health Status Change from Baseline to M24* – Short-Form General Health Survey (SF-36®) Subject-Reported Questionnaire** | | | |
| **Mental Component** | Adj. Mean Diff. [95% CI] | -0.281 [-1.473; 0.911] | 0.810 [-0.354; 1.974] |
| | P-Value | 0.6437 | 0.1725 |
| **Physical Component** | Adj. Mean Diff. [95% CI] | 0.353 [-0.591; 1.298] | 0.589 [-0.334; 1.512] |
| | P-Value | 0.4631 | 0.2106 |
| **The Change from Baseline to M24* in Binocular Visual Acuity** | | | |
| **100% Chart Score** | P-Value | 0.2312 | 0.5768 |
| **2.5% Chart Score** | | 0.1702 | 0.2078 |
| **1.25% Chart Score** | | 0.6292 | 0.7507 |

*Or termination/early discontinuation visit after Month 12

**Safety Results:**

Extent of Exposure

Of the 1,331 subjects randomized in this study, there were 450 subjects in the placebo group for a total of 785.6 subject-years, 434 subjects in the laquinimod 0.6 mg group for a total of 766.7 subject years and 447 subjects in the Avonex® for 803.2 subject-years.

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In the safety set, (1,324 subjects), mean exposure was similar across treatment groups (20.9±6.2, 21.2±6.1and 21.6±5.8 months in the placebo, laquinimod 0.6 mg and Avonex® groups, respectively). Most subjects (approximately 80%) were exposed between 21 and 24 months.

Adverse Events

Common AEs were defined as AEs reported by at least 5% of subjects in any treatment group. Common AEs reported by subjects in the laquinimod 0.6 mg group with an incidence higher than placebo by at least 1% were (placebo vs laquinimod 0.6 mg vs Avonex®): back pain (7.1% vs 10.2% vs 3.4%), nasopharyngitis (7.8% vs 9.2% vs 6.6%), arthralgia (4% vs 5.5% vs 4.1%) and depression (2.7% vs 5.1% vs 4.8%). Common AEs reported with a higher incidence in the Avonex® group compared to the placebo and laquinimod 0.6 mg groups were (placebo vs laquinimod 0.6 mg vs Avonex): pyrexia (1.6% vs 1.4% vs 11.8%) and influenza like illness (1.6% vs 1.2% vs 46.6%).

The high level term (HLT) "liver function analyses" was reported with a higher incidence in the laquinimod 0.6 mg group than the other two groups (6.7% vs 9.2% vs 8.1% in the placebo, laquinimod 0.6 mg and Avonex® groups, respectively; see below for detailed laboratory analysis). The HLT gastrointestinal and abdominal pain was also reported with a higher incidence in the laquinimod group than in the other two groups (5.1% vs 6.7% vs 3.2%).

Two deaths occurred (one due to sepsis following termination in the laquinimod 0.6 mg group and one due to cardiopulmonary failure in the Avonex® group), neither of which were considered by the investigator to be study drug related.

The overall incidence of serious AEs (SAEs) was similar in the laquinimod 0.6 mg group (7.2%) and placebo (8%) groups and was slightly lower in the Avonex® group (5.7%). No specific SAE came up as a safety signal of concern. SAEs reported by at least 2 subjects and with a higher incidence in the laquinimod 0.6 mg group compared to the placebo group (excluding MS relapse) were: chest pain (0% vs 0.5% vs 0.2% in the placebo vs laquinimod 0.6 mg vs Avonex® groups, respectively) and osteoarthritis (0.5% in the laquinimod 0.6 mg group only).

The overall incidence of early termination due to AEs was similar between the placebo (4.2%) and laquinimod 0.6 mg (4.8%) groups, and was slightly higher in the Avonex® group (5.9%).

AEs leading to early termination of at least 2 subjects in any group, and with a higher incidence in the laquinimod 0.6 mg group compared to the placebo group were abdominal pain (4 subjects vs none), upper abdominal pain (3 subjects vs none) and headache (2 subjects vs none). AEs of influenza like illness led to the early termination of 7 subjects in the Avonex® group and no subjects in the placebo and laquinimod 0.6 mg groups.

The incidence of AEs included in the standardised MedDRA query (SMQ) drug related hepatic disorders was higher in the laquinimod 0.6 mg than in the other treatment groups (6.9%, 9.9%, and 8.4% in the placebo, laquinimod 0.6mg, and Avonex® groups, respectively).

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Malignancies were reported in 2 subjects each (0.5%) in the laquinimod 0.6 mg and Avonex® groups. The number of malignancies was low and did not allow any conclusions to be drawn regarding relation to study drug.

Incidence of AEs in the system order class (SOC) Infections and Infestations occurred with similar incidence across the laquinimod 0.6 mg and placebo treatment groups and with a lower incidence in the Avonex® group (37.2%, 38.8% and 30.5%, respectively in the placebo, laquinimod 0.6 mg and Avonex® treatment groups). No specific type of infection came up as a safety signal of concern.

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

Severe AEs occurred with similar incidence between treatment groups (5.5% to 8%) and no AE was reported as severe in more than one patient in the placebo or laquinimod 0.6 mg groups (excluding MS relapse).

Most subjects with AEs were listed as having recovered or as undergoing treatment/observation. The incidence of subjects left with sequelae was lowest in the laquinimod 0.6 mg group (3.3%, 1.6% and 2.5% in the placebo, laquinimod 0.6 mg and Avonex® groups, respectively).

AEs judged by the investigator to be related to study drug were notably more common in the Avonex® group compared to the other groups (22.3% vs 27% vs 67.2% in the placebo, laquinimod 0.6 mg and Avonex® groups, respectively). The most frequently reported related AEs in the laquinimod 0.6 mg group were headache (3.3% vs 3.2% vs 7.9% in the placebo, laquinimod 0.6 mg and Avonex® groups, respectively), increased ALT (2.0% vs 2.8% vs 2.0%) and nausea (0.4% vs 1.6% vs 1.4%).

Similar proportions of males and females reported AEs in each treatment group. AEs reported more frequently by females than males in all three treatment groups were nausea and sinusitis. AEs reported more frequently by females than males in the laquinimod 0.6 mg and placebo groups but not in the Avonex® group were depression and abdominal pain.

In each treatment group, the incidence of AEs was notably higher in the USA (96.4 to 100%) vs the rest of the world (67.9 to 81.3%) and most common AEs followed the same pattern in both regions. In addition, in the laquinimod 0.6 mg group, the incidence of SAEs in the USA (14.8%) was nearly double that in the rest of the world (7.8%); the incidence of AEs leading to early termination was similar in both regions.

Clinical Laboratory

Most subjects (at least 82.2%) in each group had normal values for most laboratory parameters at baseline.

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Changes in laboratory parameters over time:

Change from baseline values for alkaline phosphatase (ALP) had a tendency to increase over time in the laquinimod 0.6 mg group and to decrease in other groups. Gamma glutamyl tranferase (GGT) had a trend towards increases in the laquinimod and Avonex® groups with inconsistent changes in the placebo group. ALT change from baseline values in all groups fluctuated over time but there was a trend towards increases early in the study with laquinimod 0.6 mg (peak increase at Visit 1/Month 1) and Avonex® (peak increase at Visit 5/Month 9) followed by decreases throughout the study. No notable increases in bilirubin were observed. Mean p-amylase changes from baseline (all increases) were generally largest in the laquinimod 0.6 mg group, followed by the Avonex® group and placebo groups.

Post-baseline shifts to abnormal biochemical values detected with a higher incidence in the laquinimod 0.6 mg group than the placebo group by at least 1% included shifts to abnormally high liver enzymes (ALP, ALT, AST and GGT), creatinine phosphokinase (CPK), p-amylase, fibrinogen, potassium and urea and shifts to abnormally low calcium, creatinine and total protein. In the Avonex® group, post baseline shifts to abnormally high values with a higher incidence than in the laquinimod 0.6 mg group were: calcium, AST, GGT and total protein.

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

No safety signal of concern was identified through analysis of thyroid hormone levels in the study. No significant trend of change in thyroid hormones over time in the study in any treatment group. Incidence of post baseline shifts to abnormally high and abnormally low thyroid hormones were lower in the laquinimod 0.6 mg group compared to the placebo group.

Liver function tests:

The incidence of post baseline shifts to levels >3xULN for ALT was higher in the laquinimod 0.6 mg group compared to the other groups. However, shifts to levels above 5xULN were lower in the laquinimod 0.6 mg group compared to placebo group. The incidence of post baseline shifts to levels >3xULN for AST was lowest with laquinimod 0.6 mg. Overall, the incidence of early termination due to elevated ALT/AST was lower with laquinimod 0.6 mg than with placebo and Avonex®. The incidence of early terminations due to elevated ALT or AST >8xULN was lowest in the laquinimod 0.6 mg group. There were no cases of liver failure and no cases of liver insufficiency as evidenced by concomitant elevations of total bilirubin. No subject in the study met Hy's law.

There were no notable trends in mean changes from baseline for all hematology parameters (apart from platelets). There was a slight trend towards decreased platelet counts in the laquinimod 0.6 mg group over the course of the study that was not observed in the other treatment groups.

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Post-baseline shifts to abnormal hematological values detected with a higher incidence in the laquinimod 0.6 mg group compared to the placebo group by at least 1% were shifts to high white blood cells (WBC, neutrophils, lymphocytes and monocytes, eosinophils) and mean corpuscular volume (MCV) and shifts to low hemoglobin (HGB, hemocrit [HCT] and red blood cells [RBC]), mean corpuscular hemoglobin volume (MCHC) and platelets. Laboratory analyses did not suggest a laquinimod-related effect of leucopenia; post baseline shifts to PCS low WBC were reported with a slightly lower incidence in the laquinimod 0.6 mg group than in the placebo and Avonex® groups.

Post-baseline shifts to PCS low HGB were reported with a higher incidence in the laquinimod 0.6 mg group than in the other two groups (3.4% vs 6.1% vs 3.6% in the placebo, laquinimod 0.6 mg and Avonex® groups, respectively) but there were no associated clinical symptoms and no subjects terminated early due to low HGB levels.

Following urinalysis, parameters with post-baseline shifts from normal to abnormal, with an incidence higher in the laquinimod 0.6 mg group compared to placebo were urine protein, ketones and blood.

Vital signs and ECG

The majority of subjects in each treatment group (at least 97.7%) had values in the normal range at baseline for SBP, DBP and pulse.

The incidence of post-baseline shifts to PCS high systolic blood pressure (SBP) and diastolic blood pressure (DBP) was lowest in the laquinimod 0.6 mg group compared to the placebo and Avonex® groups. The incidence of subjects with a shift to PCS high sitting pulse rate was similar in all groups (2.1% vs 3.0% vs 2.7% in the placebo, laquinimod 0.6 mg and Avonex® groups, respectively).

The incidence of post-baseline shifts to PCS low SPB was highest in the laquinimod 0.6 mg group (8.9%) followed by the placebo (7.6%) and Avonex® (7.3%) groups. The incidence of shifts to low post-baseline values for DBP was highest in the placebo group (16.1%), followed by the laquinimod 0.6 mg (13.8%) and Avonex® (12.9%) groups. Similarly, for pulse, the incidence of shifts to low PCS post-baseline values was highest in the placebo group (2.5%), with lower incidence reported for the laquinimod 0.6 mg (1.2%) and Avonex® (1.4%) groups. Overall, no special concerns were noted in vital signs.

At baseline, the proportion of subjects with a normal ECG was similar in each group (between 74 and 75%). The majority (at least 90%) of subjects in each group had normal ECGs throughout the study. There was a lower number of clinical alerts over the study with laquinimod 0.6 mg (5 vs 2 vs 5 alerts in the placebo, laquinimod 0.6 mg and Avonex® groups, respectively). Shifts from a normal baseline ECG to clinically significant abnormal ECG values did not occur in the laquinimod 0.6 mg group and incidence was similar in the placebo (0.4%) and Avonex® (0.2%) groups. Overall, no special concerns were noted in ECG.

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Pregnancy

Pregnancy was reported in 29 subjects (10, 8 and 11 pregnancies in the placebo, laquinimod 0.6 mg and Avonex® groups). No pregnancy of a laquinimod-treated subject resulted in fetal abnormalities. Pregnancy resulted in spontaneous abortion in one subject in each treatment group. All pregnancies which were not terminated by spontaneous or elective abortion resulted in the birth of normal infants (10 births at the time of writing this report).

The overall safety profile of laquinimod 0.6mg and Avonex® in the study was comparable. The most notable difference was in influenza like illness reported by 1.2% of laquinimod-treated subjects and by 46.6% of Avonex® treated subjects.

**Overall Summary and Conclusion**

A total of 1,331 subjects were randomized into the study: 434 subjects to laquinimod 0.6 mg, 450 subjects to placebo and 447 subjects to Avonex® (reference arm). The study was conducted in 18 countries, including Europe, South Africa, Israel and the USA.

Overall, 1,090 subjects completed the study according to protocol: 353 (81.3%) in the laquinimod 0.6 mg group, 359 (79.8%) in the placebo group and 378 (84.6%) in the Avonex® group.

A total of 241 subjects (18.1%) prematurely terminated the study with a similar incidence for the laquinimod 0.6 mg and placebo groups and a lower incidence for the Avonex® group (18.7%, 20.2% and 15.4% respectively). The most common reasons for early termination from the study were consent withdrawal (8.5%, 8.7% and 6.0%, for laquinimod 0.6 mg, placebo and Avonex®, respectively) and AEs (4.8%, 4.2% and 5.8%, for laquinimod 0.6 mg, placebo and Avonex®, respectively).

Results of the principal analysis of the primary endpoint, the annualized relapse rate during the double-blind, placebo-controlled treatment period, did not demonstrate a statistically significant treatment effect of laquinimod 0.6 mg over placebo: the risk ratio [95% CI] was 0.823 [0.664; 1.020], reflecting a 17.7% reduction in the relapse rate (p-value=0.0746). Comparison of the Avonex® reference arm with placebo yielded a risk ratio [95% CI] of 0.741 [0.596; 0.920], reflecting a reduction of 25.9% in the annualized relapse rate on Avonex® (p-value=0.0067).

A *Post Hoc* power assessment found that since sample-size calculation assumptions were disproved (placebo group annualized relapse rate and treatment effect size), the study was underpowered (42%).

Review of the baseline characteristics of the study population *post-hoc* revealed differences between the treatment groups in the mean T2 lesions volume at baseline and proportions of subjects with T1 Gd-enhancing lesions. Inclusion of these two additional covariates into a sensitivity analysis using the primary analysis model increased the reduction in ARR vs placebo to 21.3% (p-value=0.0264)

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for laquinimod 0.6 mg and to 28.6% (p=0.0021) for Avonex®.

An additional *post-hoc* analysis employing propensity score also revealed the overall bias introduced in the pre-defined primary analysis. The results of this analysis showed that when the primary analysis model was adjusted for the continuous propensity score, laquinimod 0.6 mg reduced the risk for relapses by 23.1% compared to placebo (risk ratio=0.769, nominal p-value=0.026). Similarly, when the primary analysis model was adjusted for the categorical propensity score, laquinimod 0.6 mg reduced the risk for relapses by 22.4% compared to placebo (risk ratio=0.776, nominal p-value=0.0315). Thus, the propensity scores analysis support the corrected covariate sensitivity analysis.

Sensitivity analyses using other distributional assumptions for the number of relapses (Poisson, ANCOVA or Wilcoxon) with and without additional baseline MRI covariates did not alter the results significantly from the primary analysis assumption of negative binomial distribution. Also, sensitivity analysis for missing data patterns revealed that the overall findings are robust to the amount of treatment effect preserved in the MNAR missingness data.

A *post-hoc* exploratory comparison of the ARR of laquinimod 0.6mg and Avonex® yielded a Risk Ratio of 1.102 with p=0.3887 (95%CI – 0.883-1.376) suggesting that under the BRAVO design, the apparent superiority of Avonex® over laquinimod was rejected. Further, the difference in ARR reduction (as compared to placebo) between laquinimod 0.6mg and Avonex® was 0.03 relapses a year, and it is the Sposor's assessment that it is not clinically meaningful.

Secondary endpoints were tested in an exploratory manner (at a nominal level of 5%) as the primary endpoint did not achieve statistical significance and protection against overall type-I error inflation was therefore not ensured.

The first secondary endpoint, brain atrophy as defined by the percent change in brain volume from baseline, was analyzed using baseline-adjusted ANCOVA. The results showed a 27.6% reduction in brain atrophy on laquinimod 0.6 mg versus placebo (p-value=0.0001) at Month 24 (or termination/early discontinuation visit after Month 12). Results obtained from the *post-hoc* analysis corrected for the two additional MRI parameters (baseline T2 lesions volume and indicator for subjects with T1 Gd-enhancing lesions ≥1 at baseline) were similar to those of the original analysis. For the Avonex® versus placebo treatment comparison, no appreciable difference in brain atrophy at Month 24 (termination/early discontinuation visit after Month 12) could be demonstrated, either with the original analysis or the *post-hoc* analysis corrected for the baseline MRI imbalance.

The two clinical secondary endpoints were time to confirmed progression of EDSS sustained for 3 months during the double-blind treatment period, analyzed using Cox's proportional hazards model, and disability as assessed by MSFC at Month 24 (or termination/early discontinuation visit after Month 12), analyzed using baseline-adjusted ANCOVA. Both of these endpoints, showed a reduction in the laquinimod 0.6 mg group compared to placebo (EDSS progression reduction by

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31.3% with p-value=0.0628; and MSFC z-score reduction by 77.0% with p-value=0.1505). *Post-hoc* analysis incorporating the two additional MRI covariates into the model revealed a treatment effect in favor of laquinimod 0.6 mg over placebo in EDSS progression (33.5% reduction with p-value=0.0440). Results obtained in the *post-hoc* analysis for MSFC z-score were similar to those obtained with the original analysis. Comparison between Avonex® treatment and placebo showed a reduction by 25.8% in EDSS progression (p-value=0.1269) and 65.9% reduction in MSFC z-score (p-value=0.2083). Results obtained for both secondary endpoints following *post-hoc* analyses incorporating the two additional MRI covariates were similar to those obtained with the original analysis.

In the first secondary endpoint, brain atrophy, the laquinimod 0.6mg treatment effect was larger than that of Avonex® showing a reduction of 27.6% compared to placebo whereas Avonex® showed no appreciable effect. For the clinical endpoints of EDSS progression and MSFC z-score, the treatment effects of laquinimod 0.6mg and Avonex® were comparable (p=0.7399 for EDSS and p=0.7810 for MSFC z score, respectively).

For relapse-related exploratory endpoints, numerical improvements were observed for laquinimod 0.6 mg compared to placebo for time to first confirmed relapse, proportion of relapse-free subjects and rate of severe relapses requiring hospitalization and/or administration of steroids. A benefit for Avonex® over placebo was observed more definitively for all three relapse-related endpoints.

Among MRI-related exploratory endpoints, a favorable effect of laquinimod 0.6 mg over placebo was observed for reduction of $T_1$ lesions at Month 24 but not at Month 12; there was a trend towards a reduction in the cumulative lesions count for Months 12 and 24. Treatment with Avonex® showed a reduction vs placebo in the number of $T_1$ lesions at both Month 12 and Month 24 measurements, as well as for the cumulative lesion count for Months 12 and 24.

A favorable effect of laquinimod 0.6 mg vs placebo was seen for reduction of new $T_2$ lesions at Month 12; there was a mild difference between the two groups in favor of laquinimod 0.6 mg for the cumulative new $T_2$ lesions count for Months 12 and 24. Treatment with Avonex® showed an appreciable reduction vs placebo for both endpoints. No appreciable differences between laquinimod 0.6 mg and placebo were observed for $T_2$ lesions volume, either at Month 12 or Month 24. A favorable effect for Avonex® over placebo was seen for both endpoints.

No appreciable difference between laquinimod 0.6 mg and placebo was shown for the number of new/enlarging hypointense lesions, either at Month 12 or for the cumulative hypointense lesion count for Months 12 and 24. For Avonex® there was an appreciable reduction versus placebo for both endpoints. No differences between laquinimod 0.6 mg and placebo were observed for $T_1$ hypointense lesions volume, either at Month 12 or Month 24; there was no difference between the Avonex® and placebo groups for either endpoint.

Laquinimod 0.6 mg demonstrated an appreciable reduction in brain atrophy over placebo from

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baseline to Month 12, whereas no appreciable difference between the two groups was shown between Months 12 to 24; no treatment effects on reduction in brain atrophy were seen for Avonex® over placebo for either measurement period.

For exploratory endpoints related to health status and quality of life, no appreciable differences between laquinimod 0.6 mg and placebo were observed for change from baseline to Month 24 in any of the following: subject-reported fatigue (assessed by MFIS score); any of the EQ-5D dimensions or subjects' subjective overall health assessment scores (EQ-5D-VAS); general health status assessed by SF-36 (both physical and mental component summary scores); and binocular visual acuity. Similarly, no appreciable differences could be demonstrated between Avonex® and placebo for these endpoints, with the exception of subjects' subjective overall health assessment scores (EQ-5D-VAS), for which there was a lesser decline from baseline in health status at Month 24 for subjects on Avonex® compared to those on placebo.

Overall, the BRAVO study did not meet its primary endpoint of number of confirmed relapses during the double-blind placebo-controlled treatment phase (results showed a borderline p-value) and some explanations for this result are proposed based on under power for the observed effect and *post-hoc* analyses showing baseline imbalance in favor of the placebo group. It is the Sponsor's assessment that the results obtained after a covariate analysis correcting for these baseline imbalances (effect on ARR 21.3%, p-value=0.0264) represent the true effect of laquinimod 0.6mg in this patient population more reliably.

Analysis of safety data revealed that the most frequently reported AEs (incidence >5%) for subjects in the laquinimod 0.6 mg group (with at least 1% incidence higher than placebo) were: back pain, nasopharyngitis, arthralgia and depression. Overall incidence of SAEs was similar in the laquinimod 0.6 mg (7.2%) and placebo (8%) groups and was slightly lower in the Avonex® group (5.7%). No specific SAE came up as a safety signal of concern. Overall incidence of early termination due to AEs was similar between the placebo (4.2%) and laquinimod 0.6 mg (4.8%) groups, and was slightly higher in the Avonex® group (5.9%). AEs leading to early termination of at least 2 subjects in any group, and with a higher incidence in the laquinimod 0.6 mg group compared to the placebo group were abdominal pain, upper abdominal pain and headache. AEs of influenza like illness led to the early termination of 7 subjects in the Avonex® group only. Two deaths occurred (one due to sepsis in the laquinimod 0.6 mg group and one due to cardiopulmonary failure in the Avonex® group), neither of which were considered to be study drug related.

Analysis of AEs as well as laboratory parameters did not reveal a signal suggestive of immunosuppression by laquinimod 0.6 mg. 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 PCS low WBC were reported with a slightly lower incidence in the laquinimod 0.6 mg group than in the placebo group. SAEs of malignancies were reported by two subjects in the laquinimod 0.6 mg

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group (thyroid cancer and squamous cell carcinoma) and by two subjects in the Avonex® group (thyroid cancer and colon cancer). The low number of malignancies precludes firm conclusions about possible effects of the drug.

Although the incidence of post baseline shifts to levels >3xULN for ALT was highest with laquinimod 0.6 mg, the incidence of shifts to levels >5xULN was lower than in the placebo group and the incidence of early termination due to elevated ALT/AST was lower with laquinimod 0.6 mg than with placebo and Avonex®. There were no cases of liver failure and no cases of liver insufficiency as evidenced by concomitant elevations of total bilirubin. No subject in the study met Hy's law. In the laquinimod 0.6 mg group, there was a slight trend of decrease from baseline in levels of HGB and platelets compared to the placebo group, and incidence of post baseline shifts to PCS low HGB were higher in the laquinimod group compared to the placebo group. There were no associated clinical symptoms and no subjects terminated 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 BRAVO study as a safety signal for laquinimod 0.6 mg.

There was no evidence for laquinimod-related effects on ECG, vital signs or weight. All pregnancies which were not terminated by spontaneous or elective abortion resulted in the birth of normal infants. One subject in each group had a spontaneous abortion.

It is the Sponsor's assessment that the overall risk-to-benefit ratios of the oral drug laquinimod at 0.6 mg/day and the injectable Avonex® in the study were comparable. There was no difference (p=0.3887) between ARR of the laquinimod 0.6mg and Avonex® groups and results of a comparison of the laquinimod 0.6mg treatment effect on ARR to that of the comparator Avonex®, revealed a non-clinically meaningful difference of 0.03 relapses a year. Laquinimod 0.6mg showed an effect on brain atrophy (reduction by 26.7%) whereas Avonex® did not, and results of disability secondary endpoints were comparable (p=0.7399 for EDSS and p=0.7810 for MSFC z-score, respectively). Comparison of the safety data of the two drugs in the study revealed a comparable safety profile. The most notable difference was in influenza like illness reported by 1.2% of laquinimod-treated subjects and by 46.6% of Avonex® treated subjects.

Together, efficacy and safety results of the BRAVO study support a favorable benefit-to-risk assessment for the laquinimod 0.6 mg dose and confirm the outcome seen in previous clinical trials conducted with laquinimod 0.6 mg in the treatment of patients with RRMS.