Treatment with laquinimod reduces development of active MRI lesions in relapsing MS

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Abstract—*Background:* Laquinimod is a novel immunomodulatory substance developed as an orally available disease modifying treatment in multiple sclerosis (MS). The purpose of this study was to evaluate safety, tolerability, and efficacy on MRI lesions of two different doses of laquinimod compared with placebo in patients with relapsing MS. *Methods:* In this multicenter, double-blind, randomized trial, patients with relapsing MS received 0.1 mg or 0.3 mg laquinimod or placebo as three daily tablets for 24 weeks. Gadolinium-enhanced brain MRI scans were performed at screening, every eighth week during treatment, and 8 weeks after end of treatment. The primary efficacy variable was the cumulative number of active lesions over 24 weeks. Safety measures included adverse events, physical examination, and laboratory variables. *Results:* Of 256 screened patients, 209 were randomized (67 to 74 patients per group) in 20 centers. There was a significant difference between laquinimod 0.3 mg and placebo for the primary outcome measure (mean cumulative number of active lesions reduced by 44%). In the subgroup of patients with at least one active lesion at baseline the reduction was slightly more pronounced (52%). No differences with respect to clinical variables (relapses, disability) were found. The safety profile was favorable; there were no clinical signs of undesired inflammatory manifestations. *Conclusion:* Oral laquinimod in a dosage of 0.3 mg daily was well tolerated and effective in suppressing development of active lesions in relapsing multiple sclerosis.

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Laquinimod (ABR-215062) is a novel, synthetic chemical compound with high oral bioavailability and inhibitory activity on autoimmune and inflammatory diseases in animal models. The structurally related predecessor compound roquinimex (R/Linomide) has been shown to suppress the appearance of new active lesions on MRI in phase II and III studies in multiple sclerosis (MS), but its development program had to be discontinued due to undesired inflammatory side effects (serositis, myocardial infarction).[1-5] Laquinimod was selected for clinical development based on an extensive structure-activity relationship program evaluating the biologic activity of novel quinolines.[6]

Laquinimod is an immunomodulatory substance, pharmacologically and chemically distinct from roquinimex. It has been shown to effectively inhibit development and relapses of experimental autoimmune encephalomyelitis and a favorable safety profile was demonstrated in dog studies evaluating proinflammatory effects (serosal inflammation).[6-8] Two clinical phase I studies with laquinimod showed that the compound was well tolerated by healthy volunteers and patients with MS treated for 26 consecutive days at doses up to 1.2 mg/day, but a dose limiting general inflammatory reaction, as assessed by laboratory markers, was observed at a 2.4 mg/day dose after 1 to 2 weeks of treatment.[9] Based on an integrated analysis of preclinical data and the safety and pharmacokinetics information obtained in the two clinical phase I studies, the doses used in this study, 0.1 and 0.3 mg/day, were estimated to be suitable for extended clinical testing.

All currently approved treatments for MS are given parenterally, either subcutaneously or IM, which can be associated with a variety of side reactions. As a consequence an effective oral formulation would be desirable; it could improve treatment acceptance and compliance.

Here we report the findings of a proof-of-concept study of laquinimod administered orally in patients with relapsing MS to determine the safety and efficacy of treatment on development of active brain lesions as measured by MRI.

*Members of the Laquinimod in Relapsing MS Study Group are listed in the Appendix.

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Patients and methods. This was a multicenter, double-blind, randomized, placebo-controlled study of three parallel treatment groups comprising male and female outpatients (age 18 to 65) with MS as defined by the McDonald criteria.[10] Patients had an Expanded Disability Status Scale[11] (EDSS) score of 0 to 5.5 (inclusive), and fulfilled the Lublin and Reingold criteria for relapsing remitting (RR) or secondary progressive (SP) MS.[12] The disease was to be active, defined by the presence of at least one documented clinical or subclinical (defined as a gadolinium-enhancing lesion on MRI examination or a new T2 lesion demonstrated on two consecutive MRI examinations) exacerbation in the last year or two documented exacerbations in the last 2 years (one of which could be subclinical) or the presence of gadolinium enhancement on the screening MRI scan. Patients were to have at least nine T2 lesions or a combination of at least three T2 lesions and at least one gadolinium-enhancing lesion on a T1-weighted scan at screening. Exclusion criteria defined eligibility in relation to previous immunomodulatory treatments. For example, treatment with interferon beta or glatiramer acetate should not have exceeded a total of 12 months in duration and should have been discontinued at least 6 months prior to enrollment.

Based on sample size calculations as suggested by Sormani, enrollment target was 180 patients.[13,14] The study was powered to detect a difference (50% reduction with 80% power) in the cumulative number of active lesions at week 24. The protocol was approved by the ethics committees of the participating centers before start of the study, as were protocol amendments after study initiation. Patients had to provide written informed consent.

After screening for eligibility, patients were randomized to receive either 0.1 or 0.3 mg laquinimod or placebo as three tablets once daily. Individual centers were issued with blocks of randomization numbers and corresponding tablet blisters with randomization numbers to balance the treatment allocation within each center. The screening phase, during which patients were evaluated for eligibility and had a first study MRI, was followed by a treatment period of 24 weeks and a subsequent drug-free period of 8 weeks. During treatment and follow-up MRI examinations, assessments of neurologic function (EDSS, Multiple Sclerosis Functional Composite[15] [MSFC]), quality of life (SF-36), and safety evaluations were performed every eighth week. Safety evaluations were also scheduled 2 and 4 weeks after treatment initiation; exacerbation visits took place within 72 hours after occurrence of an exacerbation.

All patients underwent MRI scanning of the brain according to a standardized protocol. MRI scans were scheduled every eighth week, less frequently than the commonly used 4-week interval. To compensate for this, three times the standard dose of gadolinium (0.3 mmol/kg) was used for the detection of enhancing lesions on T1-weighted scans.[16]

Scans were sent to a central reading center (Image Analysis Centre, Free University Medical Centre, Amsterdam) for quality assessment and evaluation. The Image analysis center as well as investigators and sponsor personnel remained blinded throughout the study.

The primary objective was to investigate the difference between the placebo group and the 0.3 mg laquinimod group in the cumulative number of active lesions over 24 weeks of treatment. The number of active lesions was defined as the sum of new gadolinium enhancement on T1-weighted images, new appearance on T2-weighted images but nonenhancing on T1-weighted images and new enlargement on T2-weighted images, but nonenhancing on T1-weighted images.

Secondary efficacy analyses included differences between pairs of treatment groups in cumulative and absolute number of active lesions and gadolinium-enhancing lesion volume on T1-weighted MRI scans at weeks 8, 16, 24 (end of treatment), and 32; lesion volume on the T2-weighted MRI scans at week 24; and number of MS exacerbations over the 24-week treatment period.

Secondary objectives also included assessment of population pharmacokinetics (PK) and safety. Population PK included analysis of each individual's systemic exposure (plasma concentrations) in relation to the development of active lesions. Safety evaluations consisted of vital signs, physical examinations, and a variety of laboratory measures. Procedures to be followed in the event of abnormal laboratory test values or suspected inflammatory events were specified in the study protocol.

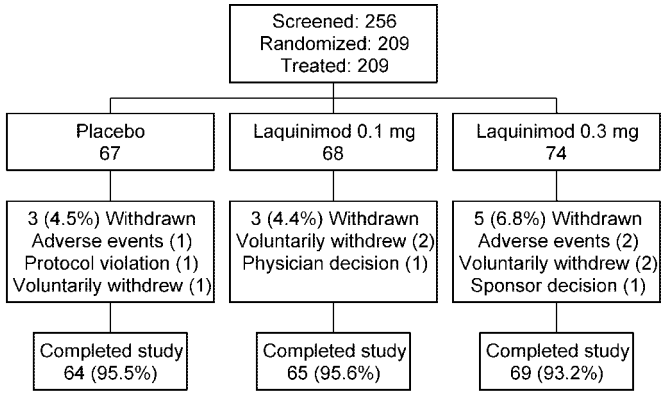

Figure 1. Patient disposition.

Analysis methods. The primary interest was the comparison between laquinimod 0.3 mg/day and placebo. The comparisons of laquinimod 0.1 mg/day vs placebo and laquinimod 0.3 mg/day vs 0.1 mg/day were of secondary interest. The endpoint for the primary objective, the cumulative number of active lesions from the MRI scans, was evaluated with analysis of covariance (ANCOVA on logged values) with treatment and baseline as independent variables. The ANCOVA, including calculation of CI based upon least square means, was performed with PROC GLM in SAS (SAS Institute, Cary, NC).

The baseline correction for lesion count consisted of the addition of gadolinium-enhancing lesions on the T1-weighted MRI at screening (week −4), new gadolinium-enhancing lesions on the T1-weighted MRI at baseline, and new and enlarging lesions (nonenhancing) on the T2-weighted MRI at baseline.

Additional analyses on the primary variable were done to test center effects and to test the subgroups of patients with RRMS and SPMS.

Other noncategorical continuous endpoints (including lesion counts) were evaluated with the same method. The (secondary efficacy) categorical variables were analyzed using the Cochran-Mantel-Haenszel (CMH) test.

Two main populations were used in the analyses of this study, the intention-to-treat (ITT) population and the per-protocol (PP) population. The ITT population consisted of all patients who were randomized to study medication. Patients were valid for inclusion in the PP population provided that they were eligible for inclusion in the study and that they had MRI assessments up to week 24 performed according to the protocol. The PP population was used for the primary analysis. Safety data were analyzed using the ITT population. For comparability with other clinical trials in MS a post hoc analysis was performed for the primary efficacy variable on patients who had at least one active MRI lesion at baseline.

Results. A total of 256 patients were screened and 209 were randomized (ITT population) and treated in 20 centers in four countries (Netherlands, Russia, Sweden, UK) (figure 1). The slight overenrollment (209 vs 180 planned) was due to an increased screening rate at many sites at the end of the patient screening period. A total of 198 (95%) of the randomized patients completed the study. The PP population consisted of 187 patients. The difference between the number of patients completing the study and the PP population was due to various protocol violations, most of them resulting in absence of MRI scans within the prespecified interval. Patients were recruited during 6 months (April 6 until October 3, 2002) and last follow-up visit for the last patient was on June 17, 2003.

Demographic characteristics were well balanced for the three treatment groups. Table 1 shows the demographic and disease characteristics of the treatment groups. In the active patient groups the number of patients with SP disease was slightly higher, and disease duration was slightly

Table 1 *Baseline demographic and disease characteristics (ITT population)*

Category	Placebo, n = 67	Laquinimod 0.1 mg/d, n = 68	Laquinimod 0.3 mg/d, n = 74	All patients, n = 209
Age, y, mean (range)	38.7 (19–59)	42.4 (19–62)	39.6 (19–61)	40.2 (19–62)
Sex, M/F	18/49	14/54	22/52	54/155
Duration of MS, y, mean (range)	5.30 (0.1–29.3)	5.82 (0.2–21.2)	5.46 (0.1–32.0)	5.52 (0.1–32.0)
EDSS, mean (range)	2.96 (0–5.5)	3.23 (1–5.5)	3.15 (0–5.5)	3.11 (0–5.5)
Type of MS, RR/SP	61/6	54/14	62/12	177/32

ITT = intent-to-treat; MS = multiple sclerosis; EDSS = Expanded Disability Status Scale; RR = relapsing-remitting; SP = secondary progressive.

longer. Baseline demographics and disease characteristics were similar for the ITT and PP populations. Table 2 shows that patients were also well matched with respect to baseline MRI status.

There was a significant difference between 0.3 mg laquinimod and placebo for the primary outcome measure (figure 2). The mean cumulative number of active lesions was 5.24 (0.3 mg laquinimod) vs 9.44 (placebo) after 24 weeks of treatment, i.e., 44% reduction by active treatment. The backtransformed adjusted means from ANCOVA were 2.3 ± 13% (geometric mean ± SEM) in the 0.3 mg group, 2.6 ± 13% in the 0.1 mg group, and 3.2 ± 13% in the placebo group. The p value for the difference between the 0.3 mg group and the placebo group was 0.0498 while there was no significant difference between the 0.1 mg group and any of the other two groups. Analysis of the primary endpoint in the subgroup of patients who had at least one active lesion at baseline (approximately 70% of the PP population) showed consistent findings (mean cumulative number of active lesions was 6.16 vs 10.54, i.e., 52% reduction, $p = 0.005$). The statistical evaluation of the reduction in cumulative number of active lesions at week 24 in the relevant populations is presented in table 3.

The ANCOVA revealed an interaction between baseline lesion activity and treatment effect. The cumulative number of active lesions was low for patients with no or low activity at baseline and the treatment groups were similar in this respect. The effect of treatment with laquinimod was greater for patients with a higher number of active lesions at baseline. The robustness of the ANCOVA on log values was checked by testing with two alternative models: a nonparametric model based on Wilcoxon statistics and a parametric model based on the negative binomial model which was used to generate the sample size in this clinical trial. The Wilcoxon statistics, testing the change from baseline, were highly significant for all three patient populations reported in table 3. The corresponding negative binomial model was significant for the PP population with active lesions at baseline, but was not for the ITT and the PP populations, probably due to a lack of fit of the model to these data. Hence, the reported ANCOVA results lay in between and in particular show where the treatment is most likely to be effective: the subset of patients with active lesions at baseline.

As can be seen in figure 2, at week 32, 8 weeks after the end of treatment, there was a trend suggestive of a rebound effect in the laquinimod 0.3 mg/day group. Additional analyses on the primary endpoint showed no treatment by center interactions and no significant differences in treatment effect between RR and SP patients.

The proportion of patients (PP population) with 0 active MRI scans during the course of treatment was 22.2% in the placebo group, 27.9% in the 0.1 mg group, and 30.2% in the 0.3 mg group. The proportion of patients with all three scans (weeks 8, 16, and 24) active was 36.5% in the placebo group, 31.1% in the 0.1 mg group, and 20.6% in the 0.3 mg group. The indicated difference between the treatment groups in number of active scans was not significant in the full PP population. However, in the subgroup of patients who had at least one active lesion at baseline, the difference in number of active MRI scans (table 4) was significant between the 0.3 mg group and the placebo group ($p = 0.024$).

The analysis comparing the cumulative volumes of gadolinium-enhancing lesions over the 24-week treatment period also showed a significant difference between laquinimod 0.3 mg and placebo; there was a suggestion of a more pronounced effect on lesion volume than on lesion numbers (data not shown). Secondary MRI variables were consistently in favor of laquinimod 0.3 mg/day as compared with placebo; for most variables the laquinimod 0.1 mg/day group was in between laquinimod 0.3 mg/day and

Table 2 *Baseline MRI status (per-protocol population)*

Category	Placebo, n = 63	Laquinimod 0.1 mg/d, n = 61	Laquinimod 0.3 mg/d, n = 63
Number of active lesions	2.44 ± 5.10	1.59 ± 2.24	1.71 ± 2.50
Number of new gadolinium enhanced lesions on T1	2.25 ± 5.00	1.48 ± 2.10	1.65 ± 2.52
Volume of gadolinium enhanced lesions on T1, mL	0.34 ± 0.67	0.37 ± 0.69	0.30 ± 0.53
Volume of lesions on T2, mL	8.79 ± 12.39	10.8 ± 9.8	12.0 ± 12.8
Patients with active lesions	45 (71)	47 (77)	44 (70)

Values are mean ± SD or n (%).

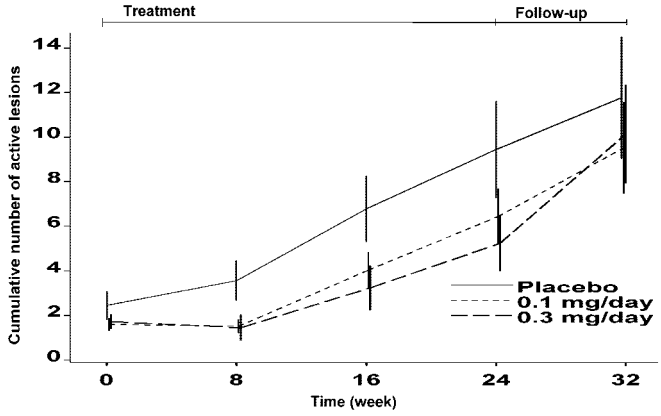

Figure 2. Cumulative number of active lesions (mean ± SE) by visit (primary endpoint).

placebo. This indicated a dose response relationship, however in most cases without significant differences between the 0.1 mg/day group and the other groups.

Only approximately one quarter of the patients in this study experienced an exacerbation during the treatment period and there was no significant difference between treatment groups for the total number of exacerbations or the proportion of patients experiencing exacerbations during treatment. EDSS, MSFC, and SF-36 (QoL) were all relatively stable over the treatment period and no significant differences between laquinimod and placebo were observed.

Table 3 *Statistical evaluation of the reduction in the cumulative number of active lesions at week 24*

	Cumulative number of active lesions		
Treatment	ITT, n = 209	PP, n = 187	PP with active lesions at baseline, n = 136
Placebo, mean (SD)	9.3 (17.2)	9.4 (17.3)	12.8 (19.4)
0.1 mg/d			
Mean (SD)	6.7 (9.7)	6.4 (9.7)	8.1 (10.5)
Reduction of mean, %	28	32	37
0.3 mg/d			
Mean (SD)	5.5 (9.7)	5.2 (9.9)	6.2 (10.5)
Reduction of mean, %	41	44	52
ANCOVA on log (cumulative number of active lesions) with log (baseline) as covariate, log of 0 set to log of 0.5			
Reduction of geometric mean (LS means), 0.3 mg/d vs placebo, %	21	28	42
95% CI of the geometric mean (LS means), 0.3 mg/d vs placebo, %	−11–44	0–49	16–61
p Value, 0.3 mg/d vs placebo	0.172	0.0498	0.0050

ITT = intent-to-treat; PP = per-protocol; ANCOVA = analysis of covariance.

Table 4 *Proportion of patients with active MRI scans during the 24-week treatment period (per-protocol population with active lesions at baseline, n = 136)*

Number of active scans	Placebo, n = 45	Laquinimod 0.1 mg/d, n = 47	Laquinimod 0.3 mg/d, n = 44
0	4 (8.9)	7 (14.9)	7 (15.9)
1	9 (20.0)	7 (14.9)	12 (27.3)
2	10 (22.2)	16 (34.0)	15 (34.1)
3	22 (48.9)	17 (36.2)	10 (22.7)

Values are n (%).

Overall, both doses of laquinimod were well tolerated in this study. The proportion of patients with adverse events was similar in the three treatment groups. There were a total of four treatment emergent and two follow-up serious adverse events (SAEs) reported in this study. Of the four treatment emergent SAEs one was in the placebo group (urinary tract infection), one in the laquinimod 0.1 mg group (brain contusion), and two in the laquinimod 0.3 mg group (iritis, burning sensation). All these patients completed treatment with study medication. Both follow-up SAEs reported were in the laquinimod 0.3 mg group (acute tonsillitis, breast cancer). During the 24-week treatment period, only two patients withdrew from the study due to adverse events, one patient in the placebo group (myocardial ischemia) and one patient in the laquinimod 0.3 mg group (muscle tightness and depression). There were no clinically relevant changes in mean hematology or chemistry values over time in any treatment group. There was a small increase in the frequency of abnormal laboratory results for erythrocyte sedimentation rate (elevated at least at one assessment in 6.0%, 13.2%, and 17.6% of patients in the placebo group, the laquinimod 0.1 mg group, and the laquinimod 0.3 mg group) and liver function tests (at least one of AP, ALT, AST, or GGT elevated at least at one assessment in 34%, 34%, and 47% of patients in the placebo group, the laquinimod 0.1 mg group, and the laquinimod 0.3 mg group). These increases were in general mild and transient and not considered to be clinically relevant. Laboratory measurements of elevated levels of C-reactive protein, considered to be indicative of undesired inflammatory reactions, did not indicate a relation to treatment (elevated at least at one assessment in 34%, 25%, and 34% of patients in the placebo group, the laquinimod 0.1 mg group, and the laquinimod 0.3 mg group).

Discussion. In this study laquinimod showed evidence of biologic activity on lesion development in a population of patients typical for relapsing MS. Treatment with a dosage of 0.3 mg/day for 24 weeks significantly reduced the cumulative number of active lesions (reduction by 44%). Patients with no active lesions at baseline did not contribute to the overall treatment effect. Thus, a subgroup analysis

of patients with baseline activity, a feature often applied as inclusion criterion in phase II MS clinical trials, showed a more pronounced effect (reduction by 52%). The observed effect size was thus in the same range as the estimated effect size used for sample size calculations, particularly for patients with baseline activity. The biologic activity of laquinimod was supported by the dose-response effect indicated for many of the MRI variables examined. A dose-response effect was also supported by the analysis of systemic exposure of laquinimod, in relation to the development of active lesions. This analysis revealed that patients with the highest systemic exposure showed the best response (data not shown). The rise in the number of active lesions which seemed to occur in both laquinimod treatment groups during follow-up (between weeks 24 and 32) after discontinuation of treatment further supported the biologic activity. Even though this observation may be interpreted as a rebound effect, it should be noted that this study was powered to detect differences in the cumulative number of active lesions at week 24 and not to detect trends over time.

The number of exacerbations in this study was relatively low (about three quarters of patients in all treatment arms were relapse-free) and EDSS, MSFC, and SF-36 were all stable over the treatment period of 24 weeks. No differences were observed in any clinical outcome measures (relapses, disability) between treatment groups.

Laquinimod showed a favorable safety profile based on clinical and laboratory variables. There was no clinical or laboratory indication of undesired inflammatory manifestations (serositis, myocardial infarction) as with the predecessor compound roquinimex.

Overall, the results from this study indicate that laquinimod has the potential to be developed as an oral treatment of MS.

Appendix: Members of the Oral Laquinimod MS Study Group

Investigators. Site 11: Prof. C.H. Polman and Dr. L. van Winsen, VU Medical Centre, Amsterdam, NL. *Site 12:* Dr. P.J.H. Jongen and Dr. Tacken, Multiple Sclerose Centrum, Nijmegen, NL. *Site 13:* Dr. E.A.C.M. Sanders, Amphia Hospital, Breda, NL. *Site 15:* Dr. R.M.M. Hupperts and Dr. E.P.M. van Raak, Academical Hospital, Maastricht, NL. *Site 21:* Prof. A.A. Skoromets and Dr. N.A. Totolyan, Pavlov Medical University, St. Petersburg, Russia. *Site 22:* Prof. Gusev and Dr. A.N. Boiko, Russian State Medical University, Moscow, Russia. *Site 23:* Prof. I. Stolyarov and Dr. A. Ilves, Institute for the Human Brain, RAS, St. Petersburg, Russia. *Site 31:* Prof. M. Sandberg, Dr. E.-M. Larsson, RN K. Lennartsson, and RN C. von Essen, University Hospital, Lund, Sweden. *Site 32:* Dr. P. Sundström, University Hospital, Umea, Sweden. *Site 33:* Prof. J. Hillert and Dr. J. Berg, Huddinge University Hospital, Stockholm, Sweden. *Site 34:* Prof. T. Olsson and Dr. F. Piehl, Karolinska Hospital, Stockholm, Sweden. *Site 41:* Dr. M.K. Sharief, Guy's Hospital, London, UK. *Site 42:* Dr. C. Constantinescu, Dr. G. Niepel, and V. Orpe, Queens Medical Centre, Nottingham, UK. *Site 43:* Dr. C. Hawkins, North Staffordshire Royal Infirmary, Stoke-on-Trent, UK. *Site 44:* Dr. K. White, Ninewells Hospital, Dundee, UK. *Site 45:* Dr. C. Young, The Walton Centre for Neurology and Neurosurgery, Liverpool, UK. *Site 46:* Prof. M. Swash, The Royal London Hospital, London. *Site 47:* Dr. D. Perkin, Charing Cross Hospital, London, UK. *Site 48:* Dr. B. Sharrack, Dr. S. Price, Dr. S. Howell, and Dr. O. Suliman, Royal Hallamshire Hospital, Sheffield, UK. *Site 49:* Dr. S. Wroe, Ipswich Hospital, Ipswich, UK.

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