ORAL LAQUINIMOD FOR THE TREATMENT OF RELAPSING-REMITTING MULTIPLE SCLEROSIS

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Laquinimod is a novel oral immunomodulator developed as a disease-modifying drug for relapsing-remitting multiple sclerosis (RRMS). This molecule was developed following a structure-activity relationship program with Roquinimex. Laquinimod has shown a marked beneficial effect in acute, chronic progressive and chronic relapsing models of experimental autoimmune encephalomyelitis. It shifts the cytokine response from Th1 to Th2/Th3 profile, reduces leukocyte infiltration to the central nervous system and halts demyelination in the spinal cord. In peripheral blood mononuclear cells, it has been shown to down-regulate the expression of major histocompatibility complex (MHC) II genes (antigen presentation) as well as a variety of genes which are involved in inflammatory processes. In addition, laquinimod has been shown to have a remarkable efficacy in animal models of other autoimmune inflammatory diseases, such as rheumatoid arthritis, inflammatory bowel disease, Guillain Barré syndrome, type-1 diabetes mellitus and lupus erythematosus.

The safety, tolerability and efficacy of laquinimod in magnetic resonance (MRI)-active MS patients were assessed in 2 placebo-controlled Phase II studies. In the first double-blind, randomized study, placebo (n=67) laquinimod 0.1 (n=68) and 0.3 mg (n=74) treated patients were assessed for a treatment period of 24 weeks. MRI was performed with triple-dose gadolinium every 8 weeks. Both doses were safe and well-tolerated. The 0.3mg daily dose, was shown to be effective in suppressing the formation of new active MRI lesions in relapsing MS patients (41% reduction; p=0.0429). A statistically significant difference between the 0.3mg dose and placebo was already observed at the first scan (week 8).

In a second randomized, double-blind, 36-weeks study, oral daily 0.3 (n=98) and 0.6 mg (n=106) laquinimod were compared to placebo (n=102). Singe-dose gadolinium MRI scans were performed at baseline, week 12 and every 4 weeks thereafter. Laquinimod 0.6mg dose showed a robust effect on MRI activity, meeting the primary and secondary endpoints of the study. It showed a 55% reduction (p=0.03) of the median number of cumulative gadolinium-enhancing T1 (Gd-T1) lesions in scans taken between weeks 24-36 (40% reduction of the corresponding mean number of Gd-T1 lesions, p=0.0048). The effect of laquinimod 0.6mg on the evolution of Gd-T1 lesions was even more pronounced between weeks 12-36 [60% effect on the median cumulative number (p=0.01), 51% effect on the mean number (p=0.0001). Statistically significant effects of similar magnitude were demonstrated on the evolution of new-T2 MRI lesions. The cumulative number of T1-hypointense lesions was reduced by 50% (p=0.0064). The 0.6mg dose showed an early effect on MRI activity also in this study: MRI active lesion counts showed a statistically significant (p=0.001) difference between the 0.6mg dose and placebo already at the first scan (week 12). Although the study was not powered to detect an effect on relapse rate, a 33% trend of reduction (p=0.09) in the annualized relapse rate was shown for the 0.6mg dose group. The 0.3mg dose (n=98) did not show an effect on MRI lesions in this study.
The early treatment discontinuation rates in this study (10.8%, 6.2% and 5.7% for the placebo, 0.3 and 0.6mg groups, respectively) indicate that laquinimod was well-tolerated. The rate of adverse events (AE) and serious adverse events (SAE) was similar in all treatment groups. In the laquinimod groups, liver enzymes were elevated in a dose-dependent and reversible manner, most of which without discontinuation of the drug.

In order to determine whether the effects observed during the Phase II study with oral daily 0.3 and 0.6 mg laquinimod, on MRI-monitored disease activity are sustained and whether the same effects achieved can be reproduced, a double-blind active extension phase was conducted. In this phase, patients who had been assigned to 0.3 or 0.6mg continued their original treatment allocation, whereas those who were treated with placebo were equally randomized to either 0.3 or 0.6mg for additional 36 weeks of treatment. Out of the 283 patients who completed the PC phase, 257 (91%) entered the extension phase to receive oral daily laquinimod 0.3 mg (119 patients) or 0.6 mg (138 patients).
In patients who switched from placebo group to active treatment, the mean number of enhancing lesions was reduced by 52% ($p<0.0007$). The reduction was significant for both patients switching to either high or to low dose laquinimod ($p<0.009$ and $p<0.03$). The proportion of enhancing lesion-free patients increased from 31% at the onset of to 47% at the end of the extension phase ($p<0.012$). A significant reduction of the mean number of enhancing lesions was also observed in patients initially treated with 0.6 (p=0.0062) and 0.3 mg (p=0.0013) laquinimod, with no further increase in the proportion enhancing lesion-free patients. No significant differences in the annualized relapse rate in patients switching from placebo to either high or low dose laquinimod. Neither new safety signals nor increase in incidence rate of AEs and laboratory abnormalities have emerged following new or prolonged exposure to laquinimod.

Based on these encouraging results, two pivotal global phase III studies, involving over 2000 relapsing MS patients were launched to evaluate the efficacy, safety and tolerability of 0.6mg laquinimod. Both studies are randomized, placebo controlled for 24 months duration. One of them has a reference arm of Interferon beta-1a (Avonex®) in order to create a benefit-risk ratio comparison with oral laquinimod 0.6 mg/d.