RATIONALE FOR LAQUINIMOD IN PROGRESSIVE MULTIPLE SCLEROSIS

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Both acute relapses and disability progression are hallmarks of RRMS

The MS disease course and progression to permanent disability relates to two clinical-pathobiological processes\(^1\)\(^-\)\(^4\)

- Acute focal inflammation from activated peripheral cells that cross the BBB; associated with relapse and active MRI lesions, which are more frequent in early RRMS.
- A progressive phase associated with diffuse inflammation trapped behind a largely intact BBB; disability accumulation increases along with patient age and disease duration.

Natural history studies suggest that disability progression to EDSS 6 and beyond is largely independent of relapse activity past the first two years from diagnosis\(^5\)\(^-\)\(^7\)

Based on laquinimod’s effects on disability and MRI indices of tissue integrity in RRMS, the rationale for trials in progressive multiple sclerosis (PMS) is made here

### Pooled ALLEGRO\(^1\) and BRAVO\(^2\) Cohort: Baseline Characteristics

<table>
<thead>
<tr>
<th></th>
<th>Laquinimod 0.6 mg N = 984</th>
<th>Placebo N = 1006</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age, years (mean ± SD)</strong></td>
<td>38.0 ± 9.3</td>
<td>38.1 ± 9.3</td>
</tr>
<tr>
<td><strong>Female Gender, n (%)</strong></td>
<td>673 (68.4)</td>
<td>689 (68.5)</td>
</tr>
<tr>
<td><strong>Time from first MS symptom, years (mean ± SD)</strong></td>
<td>7.8 ± 6.6</td>
<td>7.9 ± 6.7</td>
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<tr>
<td><strong>Time from diagnosis, years (mean ± SD)</strong></td>
<td>4.3 ± 4.9</td>
<td>4.1 ± 4.9</td>
</tr>
<tr>
<td><strong>Number of relapses in prior 2 years (mean ± SD)</strong></td>
<td>1.9 ± 1.0</td>
<td>1.9 ± 0.9</td>
</tr>
<tr>
<td><strong>EDSS score (mean ± SD)</strong></td>
<td>2.6 ± 1.3</td>
<td>2.7 ± 1.2</td>
</tr>
<tr>
<td><strong>Number of GdE T1 lesions (mean ± SD)</strong></td>
<td>1.8 ±4.5</td>
<td>1.8 ± 5.7</td>
</tr>
<tr>
<td><strong>T2 Lesions volume, cm(^3) (mean ± SD)</strong></td>
<td>9.7 ± 10.4</td>
<td>8.9 ± 9.8</td>
</tr>
<tr>
<td><strong>Normalized brain volume, cm(^3) (mean ± SD)</strong></td>
<td>1580 ± 95</td>
<td>1585 ± 93</td>
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</table>

**References:**
Laquinimod effect on CDP is large, consistent, and maintained for increasingly rigorous confirmation durations.
Laquinimod Reduces Brain Tissue Loss

- Laquinimod significantly reduced whole brain tissue loss in pivotal trials\(^1,2\)
- In an ancillary study, brain tissue preservation was evident in WM, GM, and thalamus\(^3\)

### Percent brain volume change from baseline to month 24 (adjusted mean)

<table>
<thead>
<tr>
<th></th>
<th>Placebo (n=1006)</th>
<th>Laquinimod 0.6 mg (n=984)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Change</td>
<td>-1.19%</td>
<td>-0.84%</td>
</tr>
<tr>
<td>p-value</td>
<td>&lt;0.0001</td>
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</tbody>
</table>

### References:
Laquinimod Effect on Risk of Confirmed Disability Progression is Greater than Predicted by Relapse Effect

An equation derived by Sormani et al\textsuperscript{1} predicts a treatment effect on disability (CDP) based on the actual treatment effect on annualized relapse rate (ARR)

\[
\text{log(CDP-effect)} = 0.10 + 0.63 \times \text{log(ARR-effect)}
\]

- The predicted reduction with laquinimod vs. placebo in risk of 3-month CDP was -5%
- However, the observed risk reduction was far greater: -29% (risk ratio)

- The observed treatment effect of LAQ on CDP is greater than predicted based on effect on relapse
- Different mechanisms may mediate relapse and CDP reduction by LAQ

Laquinimod Treatment Effect on CDP is only Marginally Mediated by its Effect on Relapse Reduction

Mediation was quantified as the proportion of treatment effect (PTE) using the results of logistic regression after adding first-year relapses to the model.

3-month CDP PTE for LAQ = 19%  
6-month CDP PTE for LAQ = 11%

- 3-month-CDP PTE for IFNβ-1a = 31% (in BRAVO)
- 6-month-CDP PTE for fingolimod = 60% (in FREEDOMS)

Laquinimod Reduced Disability Progression in Relapse-Free Patients

- MS disability progression continues in the absence of relapse
- LAQ reduced CDP in patients who did not relapse during the ALLEGRO and BRAVO trials

<table>
<thead>
<tr>
<th>Incidence of CDP (%)</th>
<th>Relapse-free (n=1220)</th>
<th>Relapsing (n=770)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>7.6%</td>
<td>22.1%</td>
</tr>
<tr>
<td>Laquinimod 0.6 mg</td>
<td>4.8%</td>
<td>18.9%</td>
</tr>
</tbody>
</table>

HR=0.61
(95% CI: 0.39, 0.97; p=0.032)

HR=0.73
(95% CI: 0.53, 1.01; p=0.058)
Laquinimod Efficacy was Evaluated in a Subgroup with Greater Baseline Disability

- Natural history data show once EDSS 3 is reached, disability progression becomes both more likely and more rapid\textsuperscript{1-3}
- At EDSS >3, chronic diffuse inflammation may be a more important driver of disability

<table>
<thead>
<tr>
<th>Pooled ALLEGRO and BRAVO</th>
<th>EDSS ≤3 (N=1335)</th>
<th>EDSS &gt;3 (N=655)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years), mean ± SD</td>
<td>36.5±9.1</td>
<td>41.3±8.7</td>
</tr>
<tr>
<td>Female Gender, N (%)</td>
<td>910 (68.2%)</td>
<td>452 (69.0%)</td>
</tr>
<tr>
<td>Previous MS treatment, N (%)</td>
<td>325 (24.3%)</td>
<td>163 (24.9%)</td>
</tr>
<tr>
<td>EDSS at baseline, mean ± SD</td>
<td>1.9±0.7</td>
<td>4.1±0.7</td>
</tr>
<tr>
<td>Time from MS diagnosis (years), mean ± SD</td>
<td>3.7±4.6</td>
<td>5.2±5.3</td>
</tr>
<tr>
<td>Time from first symptom (years), mean ± SD</td>
<td>6.9±6.1</td>
<td>9.7±7.2</td>
</tr>
<tr>
<td># of GdE T1 lesions, mean ± SD</td>
<td>1.5±4.2</td>
<td>2.2±6.7</td>
</tr>
<tr>
<td>Volume of T2 lesions (cm\textsuperscript{3}), mean ± SD</td>
<td>7.8±8.7</td>
<td>12.3±12.0</td>
</tr>
<tr>
<td>Baseline brain volume, mean ± SD</td>
<td>1601± 90.0</td>
<td>1547± 90.8</td>
</tr>
</tbody>
</table>

At baseline, patients in ALLEGRO and BRAVO with EDSS over 3 were older and had longer disease duration, larger T2 lesion volume, and lower brain volume.

## Disability-Related Outcomes in Patients with Baseline EDSS over 3

### Pooled ALLEGRO and BRAVO

<table>
<thead>
<tr>
<th>Outcome</th>
<th>EDSS ≤3.0</th>
<th>EDSS &gt;3.0</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>LAQ 0.6 mg, n=656 (66.7%)</td>
<td>LAQ 0.6 mg, n=328 (33.3%)</td>
</tr>
<tr>
<td></td>
<td>PBO, n=679 (67.5%)</td>
<td>Placebo, n=327 (32.5%)</td>
</tr>
<tr>
<td><strong>Time To 3-month CDP</strong></td>
<td>Hazard Ratio [CI]</td>
<td><strong>Time To 3-month CDP</strong></td>
</tr>
<tr>
<td></td>
<td>0.69 [0.50; 0.96]; p=0.0256</td>
<td>0.60 [0.38; 0.93]; p=0.0229</td>
</tr>
<tr>
<td><strong>Time To 6-month CDP</strong></td>
<td>Hazard Ratio [CI]</td>
<td><strong>Time To 6-month CDP</strong></td>
</tr>
<tr>
<td></td>
<td>0.60 [0.41; 0.88]; p=0.0088</td>
<td>0.47 [0.27; 0.82]; p=0.0083</td>
</tr>
<tr>
<td><strong>MSFC z-Score change at Month 24</strong></td>
<td>Adjusted mean difference [CI]</td>
<td><strong>MSFC z-Score change at Month 24</strong></td>
</tr>
<tr>
<td></td>
<td>-0.02 [-0.12; 0.09]; p=0.7614</td>
<td>0.25 [0.10; 0.39]; p=0.0009</td>
</tr>
<tr>
<td><strong>Brain Atrophy as defined by PBVC</strong></td>
<td>Adjusted mean difference [CI]</td>
<td><strong>Brain Atrophy as defined by PBVC</strong></td>
</tr>
<tr>
<td></td>
<td>0.34 [0.21; 0.47]; p&lt;.0001</td>
<td>0.39 [0.21; 0.58]; p&lt;.0001</td>
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</table>
Ambulation benefit in EDSS >3 Supports the CDP Effect

- At baseline, subjects in the EDSS ≤3 group completed the Timed 25-Foot Walk in a mean (SD) of 5.40 ± 5.3 seconds, and subjects in the EDSS >3 group completed the T25FW in 8.29 ± 6.81 seconds.

The T25FW data support the effect of laquinimod on CDP as an independent, relevant assessment in patients with EDSS over 3.
Conclusions

• Laquinimod-related reductions in CDP are large and robust, and cannot be explained by suppression of acute inflammation

• Clinical and MRI data demonstrate treatment effects in RRMS subgroups more likely to have progressive disease

The unique efficacy profile and mechanism of action of Laquinimod may meet the medical need for an effective treatment in progressive MS.
Laquinimod in Progressive MS: Two Parallel Placebo-Controlled Trials

Phase II MRI study (ARPEGGIO): PPMS
- 48-week Dose ranging study:
  - LAQ 0.6mg
  - LAQ 1.0 mg
  - LAQ 1.5 mg
  - placebo
- Sample size: 500 patients (125 per arm)
- Primary endpoint: Percentage brain volume change (PBVC)
- Secondary endpoints: CDP, BICAMS, number of new T2 lesions

Phase III study: Progressive MS - PPMS and SPMS
- 2 arms: LAQ 1.2 mg; placebo
- Primary endpoint: CDP
ARPEGGIO Study Design: Laquinimod for PPMS

**Screening**
- Laquinimod 0.6 mg/day
- Laquinimod 1.0 mg/day
- Laquinimod 1.5 mg/day
- Placebo daily

**Part A (Core)**
- Week 0
- Week 4
- Week 8
- Week 12
- Week 24
- Week 36
- Week 48
- Every 12 weeks
- Completion visit†

**Part B* (Data Analysis)**
- MRI Brain and C-spine
- EDSS, T25FW, 9HPT, SDMT
Questions?
Backup Slides
## Efficacy in Patients with Baseline EDSS over 3

<table>
<thead>
<tr>
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<th>EDSS ≤3.0</th>
<th>EDSS &gt;3.0</th>
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<tr>
<td><strong>Annualized Relapse Rate</strong></td>
<td>0.80</td>
<td>0.75</td>
</tr>
<tr>
<td>(LAQ 0.6 mg, n=656 (66.7%)</td>
<td>[0.67; 0.95]; p=0.0103</td>
<td>[0.60; 0.94]; p=0.0119</td>
</tr>
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<td>(PBO, n=679 (67.5%))</td>
<td></td>
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<td><strong>Time To 3-month CDP</strong></td>
<td>0.69</td>
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</tr>
<tr>
<td><strong>Disability as Assessed</strong></td>
<td>-0.02</td>
<td>0.25</td>
</tr>
<tr>
<td>by MSFC z-Score at Month 24</td>
<td>[-0.12; 0.09]; p=0.7614</td>
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</tr>
<tr>
<td><strong>Cumulative GdE T1 Lesions</strong></td>
<td>0.66</td>
<td>0.83</td>
</tr>
<tr>
<td>at Months 12 and 24</td>
<td>[0.53; 0.82]; p=0.0002</td>
<td>[0.61; 1.13]; p=0.2390</td>
</tr>
<tr>
<td><strong>Cumulative New/Enlarging T2</strong></td>
<td>0.77</td>
<td>0.75</td>
</tr>
<tr>
<td>Lesions at Months 12 and 24</td>
<td>[0.65; 0.91] p=0.0024</td>
<td>[0.59; 0.96]; p=0.0214</td>
</tr>
</tbody>
</table>
Class I–restricted CD8+ T cell up-regulated by interferon-γ

Primary oligodendroglialopathy

Oligodendrocyte

Degeneration of inner glial loop

Increased sodium-channel density

Postsynaptic neuron

Terminal axon ovoid

Normal myelin sheath

Remyelinated areas

Glial growth factors?

Oligodendrocyte precursor cell

Proliferation Migration Differentiation Remyelination

Systemic circulation

Activated antigen-presenting cell (astrocytes, microglia, macrophages)

CD4+ Th1 cell

CD4+ Th2 cell

CD4+ T cell

Activated B cell

Antibodies

Interleukin-12

Interferon-γ

Antibody-mediated remyelination

Antibody/complement-mediated injury

Cytokine-mediated injury

E-selectins up-regulated

ICAM-1, VCAM-1

Putative MS antigen

TCR

CD4+ Th1 cell

CD4+ Th2 cell

CD4+ T cell

B7G-1, B7-2

CD28

CTLA-4

Anergy

Antiinflammatory signaling

Interleukin-4, 10, 13

B7G-1, B7-2

CD28

CTLA-4

Anergy

Class II MHC molecule

Putative MS antigen

TCR

CD4+ Th1 cell

CD4+ Th2 cell

CD4+ T cell

Activated antigen-presenting cell (astrocytes, microglia, macrophages)

TNF-α, Interferon-γ

B7G-1, B7-2

CD28

CTLA-4

Anergy

Class II MHC molecule

Putative MS antigen

TCR
Effect of Laquinimod on Demyelination in the Cuprizone Model

Laquinimod has direct effects on peripheral immune cells and within the CNS.

Laquinimod affects the amount of tissue damage within focal lesions and the diffusely altered brain tissue.

Astrocyte and microglia activation are major factors in the pathogenesis of tissue damage in lesions and the diffusely abnormal brain tissue.

Laquinimod reduces activation of CNS-resident cells - astrocytes and microglia - via interference with the NFkB pathway.

Laquinimod MoA supports the clinical results demonstrating reduction of neurodegeneration and delay in disability progression.