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Effects of Early Treatment of Progressive MS

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Mount Sinai School of Medicine
New York, NY
20 Years of MS Clinical Course in 20 Seconds: The Phenotypes

RIS  CIS  RRMS  SPMS  Active SPMS

CIS = clinically isolated syndrome; MS = multiple sclerosis; RIS = radiologically isolated syndrome; RRMS = relapsing-remitting MS; SPMS = secondary progressive MS.

20 Years of MS Clinical Course in 20 Seconds: Disability Trajectory

Maximizing Brain Health and Neurological Reserve in MS

• In untreated MS, greater brain reserve (estimated with maximum lifetime brain growth [MLBG]) is protected against physical disability over 5 years ($P=.029$)

• **Absolute change in EDSS scores:**
  – Patients with smaller MLBG showed worse EDSS change ($0.91 \pm 0.71$) than patients with larger MLBG ($0.42 \pm 0.87$)

EDSS = Expanded Disability Status Scale.
Treatment May Delay Development of SPMS in High-Risk Patients

• Data from 1178 patients with a relapsing form of MS at onset and at least 10 years of disease duration, treated (59%) or untreated with DMTs.

• Risk of secondary progression was significantly lower in patients treated with DMTs, regardless of the initial prognosis predicted by BREMS.
  
  – Criterion for progressive disease was continuing deterioration (for at least 1 year) severe enough to lead to an increase of at least 1 point on the EDSS, without substantial remission or exacerbation.

BREMS = Bayesian risk estimate for multiple sclerosis; DMTs = disease-modifying therapies.
Long-term Observational Study on Effects of Early Treatment on Conversion to SPMS

Treatment With DMT Versus No Treatment

HR: 0.26 (95% CI: 0.15-0.45); P<.001

<table>
<thead>
<tr>
<th>Time From Matching, years</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
<th>8</th>
<th>9</th>
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<th>11</th>
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<tbody>
<tr>
<td>No Treatment</td>
<td>47%</td>
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<td></td>
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<tr>
<td>Treatment</td>
<td>19%</td>
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No. with follow-up data

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<tbody>
<tr>
<td>No treatment</td>
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<td>164</td>
<td>164</td>
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<td>144</td>
<td>116</td>
<td>93</td>
<td>78</td>
<td>61</td>
<td>43</td>
<td>28</td>
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</tbody>
</table>

CI = confidence interval; HR = hazard ratio.
Long-term Observational Study on Effects of Early Treatment on Conversion to SPMS

Treatment With DMT
Before Versus After 5 Years of Disease Onset

HR: 0.77 (95% CI: 0.61-0.98); P=.03

Proportion converted to SPMS

Time From Matching, years

No. with follow-up data
>5 years 38 38 38 38 36 31 23 15 11
≤5 years 120 120 120 119 115 102 77 60 44

Big MS Data Network: When to Start DMT

• Combined MSBase (Australia), Danish/Italian/Swedish national registries, OFSEP (France), and real-world data (BMSD network)

• DMT initiation in relapsing MS; pairwise propensity score matching analyses
  – 10 distinct cutoffs for treatment, using 0.5-year intervals for early versus delayed treatment
  – Time to 12 months confirmed EDSS worsening

BMSD = Big Multiple Sclerosis Data; MSBase = MSBase Neuro-Immunology Registry; OFSEP = Observatoire français de la sclérose en plaques.
Iaffaldano P, et al. Presented at: ECTRIMS 2018; October 10-12, 2018; Berlin, Germany. Abstract #204.
Big MS Data Network: When to Start DMT (cont’d)

- N=11,934 patients with relapsing MS; median follow-up: 13.2 years (N=149,636 screened)
- 34.9% (N=4138) reached disability ≥3 EDSS score
- 28% lower risk of EDSS disability confirmed at 12 months when DMT started within 6 months of disease onset ($P=0.003$)
  - No other significant comparison

**Conclusion:** Optimal DMT timing is within 6 months of disease onset

Iaffaldano P, et al. Presented at: ECTRIMS 2018; October 10-12, 2018; Berlin, Germany. Abstract #204.
**Primary Endpoint:** Significant Reduction in 12-week CDP

**Key Secondary Endpoints:**
- 24-week CDP
  - 25% reduction in risk of CDP ($P=0.0365$)
  - Progression rate of walking time
  - 29% reduction versus placebo ($P=0.0404$)
  - Rate of BVL
    - 17.5% reduction versus placebo ($P=0.0206$)
  - T2 lesion volume
    - 7.4% increase on placebo
    - 3.4% decrease on ocrelizumab ($P<0.001$)

**Safety:** Similar incidence of AEs and severe AEs with ocrelizumab and placebo. Most common events were mild-to-moderate infusion-related reactions. Possible malignancy signal.

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**ORATORIO Phase 3 Study Results:**

Ocrelizumab in PPMS

AEs = adverse events; BVL = brain-volume loss; CDP = composite disability progression; PPMS = primary progressive MS.

Siponimod: sphingosine 1-phosphate receptor modulator indicated for the treatment of relapsing forms of MS, to include clinically isolated syndrome, relapsing-remitting disease, and active secondary progressive disease, in adults.
Figure from Prescribing Information: https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/209884s000lbl.pdf
Advancing Science in Imaging of Progressive MS

Guy J. Buckle, MD, MPH
Director of Neuroimaging Research
MS Institute at Shepherd Center
Atlanta, GA
Conventional MRI in MS

FLAIR

T1 Gd Disease Activity

T2 BOD

T1 Black holes strongest correlation progression of disability

BOD = burden of disease; Gd = gadolinium; MRI = magnetic resonance imaging; MS = multiple sclerosis.

Images courtesy of Guy J. Buckle, MD, MPH.
High-Field MR Imaging 3T

• 3D MPRAGE improves classification of cortical lesions in multiple sclerosis
  – 11 patients with MS with previously identified cortical lesions were scanned using DIR, PSIR, and 3D MPRAGE
  – 119 lesions were identified as either intracortical or mixed on DIR/PSIR
    ▪ In 89 cases, MPRAGE confirmed the classification by DIR/PSIR
    ▪ In 30 cases, MPRAGE overturned the original classification

3D = 3-dimensional; DIR = double-inversion recovery; PSIR = phase-sensitive inversion recovery.
In Vivo Quantifying Tissue Damage: Measuring Neurodegeneration

- Atrophy
- MTR
- fMRI
- DTI
- OCT
- $^1$H-MRS
- Tractography
- Quantitative cord imaging
- SWI

DTI = diffusion tensor imaging; fMRI = functional MRI; MRS = magnetic resonance spectroscopy; MTR = magnetization transfer ratio; OCT = optical coherence tomography; SWI = susceptibility weighted imaging.
Brain Atrophy

ACTRIMS 2019 Forum
Abstracts can be found here:
https://actrims.confex.com/actrims/2019/meetingapp.cgi/Search/0?sort=Relevance&size=50&page=1&ModelType=Paper
Brain Atrophy in MS

• Brain atrophy represents the cumulative effect of
  – Demyelination and axonal loss
  – Diffuse, nonfocal tissue damage

• Global brain atrophy; brain tissue decreases at an approximate mean rate of
  – 0.1% to 0.32% per year in normal controls
  – 0.7% to 2.0% per year in patients with MS

Brain atrophy starts at age 18 to 20 years and continues at a steady rate of 0.2% to 0.3% per year between the ages of 20 and 50 years. It then accelerates to rates of 0.5% to 0.6% per year after age 55 to 60 years and is even higher in the 8th and 9th decades of life.

In multiple sclerosis, the rate of atrophy is up to 0.8% to 1% per year.

Figure 1. Cross-sectional plot of brain volume in nondemented adults over the adult life span.

Normalized Whole Brain Volume

BPF = Brain parenchymal fraction

**BPF as a Measure of Brain Atrophy**

*Age matched subjects in sixth decade*

<table>
<thead>
<tr>
<th>Healthy control</th>
<th>RRMS</th>
<th>RRMS</th>
<th>SPMS</th>
</tr>
</thead>
<tbody>
<tr>
<td>BPF 0.89</td>
<td>BPF 0.84</td>
<td>BPF 0.80</td>
<td>BPF 0.70</td>
</tr>
<tr>
<td>EDSS 1.5</td>
<td>EDSS 4.0</td>
<td>EDSS 6.5</td>
<td></td>
</tr>
<tr>
<td>DD 5 years</td>
<td>DD 10 years</td>
<td>DD 18 years</td>
<td></td>
</tr>
</tbody>
</table>

BPF = brain parenchymal volume; DD = disease duration; EDSS = Expanded Disability Status Scale; RRMS = relapsing-remitting MS; SPMS = secondary progressive MS.

The SIENA software provides accurate, fully automatic measurement of atrophy using edge motion, with variability of <0.2%

SIENA = Structural Image Evaluation using Normalisation of Atrophy
Image courtesy of Guy J. Buckle, MD, MPH.
Figure illustrating typical cortical grey matter atrophy in multiple sclerosis (MS). Both panels display an inflated cortical surface produced by FreeSurfer software, overlayed with vertex-wise cortical thickness (grey: < 2 mm; red: 2 mm; yellow: > 4 mm)

HC – healthy control
GM Versus WM Brain Atrophy


GM = gray matter; WM = white matter.
Selective Thalamic Atrophy in MS

- Thalamus
  - 17% lower
  - $d = 1.2$
- Whole brain
  - 3% lower
  - $d = 0.6$

Thalamic Atrophy Related to Cognition in MS

- Cognitive performance in all domains was moderately to strongly related to thalamic volume in the MS group
  - $r = 0.658$, $P<.0001$ (SDMT)
  - $r = 0.658$, $P<.0001$ (SDMT)

SDMT = Symbol Digit Modalities Test.
Brain Atrophy: The Bottom Line

• MS is a destructive disease
• Atrophy/tissue loss begins early in MS
• Atrophy is continuous/progressive
• Occurs in most patients with MS
• Occurs even when only mild disability is present
• Atrophy is clinically relevant
• Time is brain (atrophy is partially preventable)
Ultra High-Field (7T+) Imaging
Improved Contrast at 7T – Normal Volunteer

195 X 250 microns in plane

Images courtesy of Guy J. Buckle, MD, MPH.
Sagittal View at 7T – MS Patient

Images courtesy of Guy J. Buckle, MD, MPH.
Gray Matter at 7T
High Field MR Imaging 7T

• See examples of this in vivo imaging of cortical pathology in MS using ultra-high field MRI at the reference link below

White Matter at 7T
Multiple Sclerosis Lesions

Image courtesy of Guy J. Buckle, MD, MPH.
Persistent Phase Rims in a Gadolinium-enhancing Lesion in a Patient With Secondary Progressive Multiple Sclerosis

Perivenous Distribution of Multiple Sclerosis Lesions: 3 T FLAIR

3 T FLAIR* (combined T2*-weighted MRI and fluid-attenuated inversion recovery)
Spinal Lesions in MS – MRI Findings

- Increase sensitivity for MS diagnosis
- Cervical cord most common
- Cord atrophy as marker of disability
- Acute/subacute lesions:
  - Focal, oval, bright T2WI
  - 1 to 2 cord levels
  - Lateral aspect of cord, <1/2 diameter
  - Enhancing 14% to 33%
- Chronic: May become confluent

MRI of Acute Spinal MS

FSE = fast spin echo.
Cervical Cord Atrophy in MS

RRMS, EDSS 1.5, DD 2 years
Area: 85 mm$^2$

PPMS, EDSS 7.0, DD 8 years
Area: 46 mm$^2$

Images courtesy of Dr. F. Barkhof.
Spinal Cord Atrophy in SPMS

Whole Spinal Cord Volume

Operator time = 5 minutes

Images courtesy of Guy J. Buckle, MD, MPH.
Continuous Brain and Cord Imaging

Image courtesy of Guy J. Buckle, MD, MPH.
Diffusion Tensor Imaging (DTI)

Color on DTI-Overlay | Orientation              | Example                                           |
----------------------|--------------------------|---------------------------------------------------|
Red                   | Right-Left               | Callosal fibers                                   |
Green                 | Anterior-Posterior       | Fornix, cingulum                                  |
Blue                  | Inferior-Superior        | Internal capsule, corona radiata, corticospinal tract |

Images courtesy of Dr. Flavia Nelson.
Diffusion Tensor Imaging (DTI) at 3T

Image courtesy of Dr. Flavia Nelson.
DTI Tracks of a Healthy Subject Versus MS

DTI allows measurement of fractional anisotropy (FA), which reflects the degree to which the diffusion of water molecules follows 1 direction versus many. When there is damage to axons or their myelin sheaths, there may be increased diffusion of water across the white matter tract and a decreased FA.

Images courtesy of Dr. Flavia Nelson.
Diffusion Tensor Imaging (DTI) at 3T


Quantitative spinal cord MRI measures
Conclusions

• MRI is a powerful and sensitive tool for diagnosing MS but lacks pathological specificity.
• MRI is a valuable surrogate marker of biological disease activity and severity as well as treatment response.
• The continuing worsening of MRI findings, even if clinically silent, impact long-term clinical outcomes.
• Conventional MRI measures (T2 lesions and Gd enhancement) represent only the “tip of the iceberg,” in terms of disease activity.
• Newer techniques hold greater promise for following both inflammation and neurodegeneration throughout all stages of the disease process.
DMT Updates in Progressive MS

Patricia K. Coyle, MD, FAAN, FANA
Professor and Vice Chair (Clinical Affairs)
Department of Neurology
Director, Multiple Sclerosis Comprehensive Care Center
Stony Brook University Medical Center
Stony Brook, NY
DMT Updates in Progressive MS

- Ocrelizumab
- Siponimod
- Agents in late-stage development (biotin, ibudilast, simvastatin)
- CNS repair strategies

CNS = central nervous system; MS = multiple sclerosis.
Ocrelizumab PPMS Approval

**FDA**
- Adults with PPMS

**EMA**
- Adults with early PPMS (in terms of disease duration, level of disability) and with neuroimaging features characteristic of inflammatory activity (new/↑ T2, contrast lesions)
  - Early active PPMS

**Notes:**
- EMA = European Medicines Agency; FDA = US Food and Drug Administration; PPMS = primary progressive multiple sclerosis.
Primary Endpoint: Significant Reduction in 12-Week CDP

Time to 12-week Confirmed Disability Progression

- Placebo (n=244)
- Ocrelizumab 600 mg (n=488)

24% reduction in risk of CDP
HR (95% CI): 0.76 (0.59, 0.98); p=0.0321

ORATORIO Phase 3 Study Results: Ocrelizumab in PPMS
CDP = composite disability progression.
## Effect of Gadolinium-enhancing Lesions on Efficacy of Ocrelizumab in PPMS

<table>
<thead>
<tr>
<th>Primary endpoint</th>
<th>Placebo (n=244)</th>
<th>Ocrelizumab 600 mg (n=488)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Gadolinium-positive</td>
<td>Gadolinium-negative</td>
</tr>
<tr>
<td>Confirmed disability progression for at least 12 weeks</td>
<td>27/60</td>
<td>68/183</td>
</tr>
<tr>
<td>Patients with event (n)</td>
<td>Hazard ratio vs placebo (95% CI)</td>
<td>0.65 (0.40-1.06)</td>
</tr>
</tbody>
</table>

CI = confidence interval.
Sustained Reduction in Disability Progression in Patients With PPMS Treated With Ocrelizumab

• After 5.5 years (264 weeks) of follow-up, proportion of patients with disability progression in EDSS and 9HPT was lower in patients who initiated ocrelizumab treatment earlier compared with patients initially receiving placebo.

Open-label extension phase of the ORATORIO trial.
EDSS = Expanded Disability Status Scale; 9HPT = 9-Hole Peg Test.
ORATORIO Trial Considerations

• CNS penetration <0.1%
  – Cannot have primary effect on neurodegeneration
  – Represents anti-inflammatory impact

• The trial involved patients:
  – Aged ≤55 years
  – Ambulatory PPMS (EDSS ≤6.5)
  – MS duration ≤15 years
  – +CSF (inflammatory marker)

CSF = cerebrospinal fluid.
Ocrelizumab Post-Marketing Data

• Ocrelizumab depletes B cells, as well as CD3+ and CD20+ T cells
  – 3% to 5%
  – Enriched for CD8+ and CD45RO+ cells
  – Highly activated, producing proinflammatory cytokines
• A minority of individuals develop low IgG (8.5%) without apparent infections

ACTRIMS 2019: Myelin water fraction (MWF) in OPERA II substudy (N=56) showed stability/↑ with ocrelizumab versus ↓ with IFNβ

IFN = interferon; IgG = immunoglobulin G.
Ocrelizumab Post-Marketing Data (cont’d)

• Multiple current/new studies
  – Shorter infusion times (1.5 to 2 hours)
  – Subcutaneous (planned doses 40 mg → 1200 mg)
  – ORATORIO-HAND (EDSS 3 to 8; primary outcome 9HPT)
  – At least 2 studies will address sex-based issue

Siponimod

• Oral, second-generation S1P receptor modulator
  – Not a prodrug
  – $T_{1/2}$ ~30 hours (washout 7 days)
  – S1P receptors 1 and 5

• Approved for relapsing forms of MS (CIS, RRMS, active SPMS)

• Screening involves blood (CYP2C9 genotype, CBC, VZV-IgG, hepatic panel), ophthalmic evaluation, EKG, review drugs that slow HR/AV conduction

AV = atrioventricular; CBC = complete blood count; CIS = clinically isolated syndrome; EKG = electrocardiogram; HR = heart rate; RRMS = relapsing-remitting MS; S1P = sphingosine 1-phosphate; SPMS = secondary progressive MS; VZV-IgG = varicella zoster virus-immunoglobulin G.

Siponimod

- CYP2C9*3/*3 genotype excluded (≤0.4% of Caucasian individuals); CYP2C9*1/*3 and *2/*3 genotypes maintenance dose is 1 mg (10% to 15%)

- Dose titrated (0.25 mg → 2 mg) over 6 days

- First-dose monitoring is recommended for sinus bradycardia, first- or second-degree AV block, history of myocardial infarction or congestive heart failure

EXPAND Study

- Entered N=1651 patients with progressing SPMS
- More severe cohort than IFNβ-1b phase 3 SPMS trials
- Able to show 21% ↓ in confirmed (12 week) EDSS progression (26% vs 32% progressed, $P=0.013$)
- Worked best in younger patients with MS, shorter disease duration, ↓ EDSS, prior relapses, baseline contrast lesions, DMT-naïve
Biotin (Vitamin B7)

- Ubiquitous water-soluble vitamin
- Essential coenzyme for carboxylases (energy metabolism, FA synthesis)
- High biotin doses could
  - Activate Krebs cycle in axons (↑ ATP)
  - Activate Krebs cycle in oligos (↑ citrate for lipid synthesis)
  - Activate ACC1, ACC2 (rate-limiting enzymes in LCFA synthesis for myelin)
  - Reverse virtual hypoxia, trigger remyelination

ACC = acetyl-coenzyme A carboxylase; ATP = adenosine triphosphate; FA = fatty acid; LCFA = long-chain fatty acid.
High-Dose Biotin in Progressive MS

- **Phase 3 (MS-SPI) trial of MD1003**
  (high grade/concentration of biotin 300 mg QD; equivalent of 30 tablets)
  - N=154 patients with progressive MS (PPMS, SPMS); EDSS 4.5 to 7; randomized to biotin (N=103) or placebo (N=51)

- **Primary outcome improvement at 9 months, confirmed at 12 months** (EDSS improved, or 25-foot walk time improved 20%)
  - Intent-to-treat (ITT) 12.62% vs 0% (P=.0051)
  - Per protocol 14.9% vs 0% (P=.0093)

High-Dose Biotin in Progressive MS (cont’d)

- Phase 3 placebo trial in optic neuritis permanent vision loss: failed (chronic vs acute optic neuropathy seemed to respond)¹

- Current phase 3: SPI2

SPI2 Trial

- Phase 3 randomized, double-blind, placebo-controlled trial for at least 15 months
  - Open-label extension up to 12 months
- N=642 progressive MS (PPMS, SPMS) randomized to biotin 100 mg PO 3x daily or placebo
- **Primary outcome:** \(\downarrow\) EDSS or 25 FTW at Month 12, confirmed at Month 15
- **Secondary outcome:** time to confirmed EDSS progression

Effect of MD1003 in Progressive Multiple Sclerosis (SPI2). ClinicalTrials.gov Identifier: NCT02936037.
Ibudilast

- Oral small-molecule inhibitor: phosphodiesterase 4 and 10; Mφ migration inhibitory factor, tau-like receptor 4
  - ↓ proinflammatory cytokines, ↑ neurotrophic factors, attenuates activated glia
- Approved in Japan/Korea for post-stroke dizziness, asthma
- **Phase 2B SPRINT trial** entered N=255 progressive MS (PPMS, SPMS) randomized to up to 50 mg 2x daily (N=129) vs placebo (N=126) for 96 weeks
  - Could be on IFNβ, glatiramer acetate

Ibudilast (cont’d)¹

• Whole-brain atrophy ↓ 48% vs placebo
  (-0.0010 vs -0.0019 annually, \( P = .04 \))
  – Measured by BPF
  – Cortical atrophy ↓ 80% (\( P = .004 \))

• Significant impact on MTI, but not DTI; no impact on OCT RNFL thickness (these were not adjusted for multiple comparisons)

• Well tolerated (gastrointestinal, headache, depression)

• Post hoc analysis indicates PPMS drove atrophy effect²

BPF = brain parenchymal fraction; DTI = diffusion tensor imaging; MTI = magnetization transfer imaging; OCT = optical coherence tomography; RNFL = retinal nerve-fiber layer.

Simvastatin

• **Phase 2 MS-STAT trial:**
  - N=140 SPMS
  - Randomized to 80 mg simvastatin vs placebo
  - Annual brain volume loss -0.288 vs -0.584; adjusted difference -0.254 ($P= .003$), 43% reduction

• **Current phase 3 SPMS trial (MS-STAT2)**
  - N=1180 SPMS
  - Will take 6 years to complete
  - 80 mg PO daily

CNS Repair Strategies

• Enhance relapse recovery
• Improve fixed deficit
• General strategies to improve CNS reserve (wellness; comorbidity management)
CNS Repair Strategies (cont’d)

- Block inhibitory factors
  - Opicinumab (humanized MAb to LINGO-1)
  - Elezanumab (humanized MAb to repulsive guidance molecule A)
- Stem cell therapy (especially mesenchymal)
- Epstein-Barr virus-specific autologous T cells
- Clemastine (antimuscarinic; repurposed antihistamine)
- Liothyronine
  - Proposed selective thyroid hormone agonists (sobetirome, Sob-AM2)

MAb = monoclonal antibody.
Opicinumab

• Blocking LINGO-1 promotes oligodendrocyte differentiation and remyelination
• MAb given IV monthly

• Phase 2 RENEW trial in acute optic neuritis (N=82 ITT)
  – Full-field visual evoked potential improved (prespecified per protocol significant, ITT nonsignificant)

• Phase 2B SYNERGY trial (N=418) on intramuscular IFNβ-1a ± opicinumab (3, 10, 30, 100 mg/kg IV) or placebo
  – Negative (U-shaped inverted response, ~25% responders)

• AFFINITY trial (N=236)
  – Add on opicinumab 750 mg IV vs placebo to background DMT
  – Primary outcome overall response score (EDSS, 25 FTW, bilateral 9HPT)

IV = intravenous.
Elezanumab (ABT-555)

- Human MAb to repulsive guidance molecule A (RGMa)
- RGMa inhibits neurite growth by binding to the neogenin receptor, regulator of cell death
- Phase 1 double-blind, randomized, escalating multiple dose (150 mg, 600 mg, 1800 mg), 29-week study
  - N=20 (18 remitting multiple sclerosis, 2 SPMS)
  - Well tolerated; no worsening
- Current phase 2 trial N=165 relapsing forms of MS on standard of care
  - IV elezanumab (2 doses) vs placebo
  - 52 weeks overall response score

Summary

• We have begun the era of progressive MS DMTs
• CNS repair strategies are in development
• They involve multiple approaches
  – Including remyelination, blocking inhibitory factors, replacing cells, brain–machine interfaces, advanced rehabilitation (eg, robotic exoskeleton suits)
• The future looks bright!
Please take a moment to take the posttest to receive CME credit.

Thank you for joining us.