2013 Emerging Science Abstracts

The Emerging Science abstracts were presented at the 2013 AAN Annual Meeting. Abstracts qualify for Emerging Science presentations by having key aspects of research conducted after the October 15th abstract submission deadline and must be new and of sufficient scientific importance to warrant expedited presentation and publication. The Science Committee is committed to presenting the best neuroscientific research at the Annual Meeting; 12 abstracts were accepted for dual presentation and 9 were accepted as poster presentations.

Novel CSF biomarkers for frontotemporal lobar degeneration with lesions immunoreactive to TDP-43 (FTLD-TDP)

William Hu, MD, PhD; Kelly Watts, MS; Murray Grossman, MD, FAAN; Jonathan Glass; James Lah, MD; John Trojanowski, MD, PhD; Allan Levey, MD, PhD

OBJECTIVE: To validate five previously identified CSF biomarkers for FTLD-TDP, and to report a novel, robust, stand-alone CSF biomarker for FTLD-TDP. **BACKGROUND:** There is currently no reliable way to predict the underlying FTLD pathology while the patients are still living, and an ante-mortem biomarker for one of the main FTLD subtypes (FTLD-TDP or FTLD-Tau) can significantly enhance the pathology-based FTLD diagnosis and clinical trials for FTLD-TDP and FTLD-Tau. **DESIGN/METHODS:** Two independent cohorts of patients with frontotemporal dementia (FTD) were recruited independently from Emory University (Atlanta, GA) and University of Pennsylvania (Penn; Philadelphia, PA) to undergo CSF analysis. These include patients with high likelihood FTLD-TDP (FTD patients with amyotrophic lateral sclerosis or FTD patients with mutations in PGRN or C9ORF72) and patients with high likelihood FTLD-Tau (FTD patients with progressive supranuclear palsy or FTD patients with mutations in MAPT). Levels of five CSF previously identified proteins were measured, along with levels of total Tau (t-Tau) and Tau phosphorylated at threonine 181 (p-Tau₁₈₁). **RESULTS:** 29 Emory patients and 40 Penn patients participated in the study, including 43 patients with high likelihood FTLD-TDP and 26 patients with high likelihood FTLD-Tau. Using the Emory cohort, we validated the group level differences in CSF cotaxin-3, Fas, and IL-23 ($p < 0.01$) previously identified using the Penn cohort. We also identified the ratio of p-Tau₁₈₁ to t-Tau (p/t-Tau ratio) to be significantly lower in Emory FTLD-TDP cases compared to Emory FTLD-Tau and AD cases. Using the Penn cohort as a validation set, p/t-Tau ratio alone is sufficient to identify FTLD-TDP with 88% sensitivity and 73% specificity. **CONCLUSIONS:** CSF biomarkers have the potential of accurately identifying FTLD-TDP, and further development of this and other FTLD-TDP biomarkers will significantly accelerate the ante-mortem prediction of FTLD-TDP pathology and design of substrate-specific FTLD clinical trials.

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Safety and efficacy of ORM-12741 on cognitive and behavioral symptoms in patients with Alzheimer's disease: A randomized, double-blind, placebo-controlled, parallel group, multicenter, proof-of-concept 12 week study

Juha Rouru; Keith Wesnes; Jutta Hänninen; Michael Murphy, MD, PhD; Henry Riordan, PhD; Juha Rinne, MD, PhD, FAAN

OBJECTIVE: The primary objectives were to evaluate safety, tolerability and efficacy of ORM-12741 as add-on therapy in patients with Alzheimer's disease (AD). **BACKGROUND:** ORM-12741 is a highly potent and selective alpha-2C adrenoceptor (AR) antagonist that has demonstrated efficacy in rodent models suggesting beneficial effects on cognition and behavioral symptoms in AD, as well as good tolerability across seven phase I studies. This is the first report of a selective alpha-2C AR antagonist in AD patients. **DESIGN/METHODS:** This was a phase IIa, randomized, double-blind, placebo-controlled study of 100 moderate AD patients (MMSE scores 12-21) with behavioral symptoms (Neuropsychiatric Inventory (NPI) score of ≥ 15). Patients were allocated to two flexible dose levels of either 30 to 60 mg or 100 to 200 mg of ORM-12741 or matching placebo twice daily for 12 weeks as add-on to their stable cholinesterase inhibitor therapy ($\pm$ memantine). Efficacy was assessed primarily with computerized tests from CDR System, from which standard composite scores were derived including: Quality of Episodic Memory (QEM), Quality of Working Memory (QWM), Quality of Memory (QM), Speed of Memory and Power of Attention. NPI was assessed to quantify the effects on behavioral and psychological symptoms. **RESULTS:** Clear and statistically significant positive treatment effects were noted for ORM-12741 on QEM ($p=0.03$) and QM ($p=0.0127$) compared to the placebo group over the 12 week treatment period with no clear difference in efficacy between the two active dose groups. In addition, a positive trend was noted for both QWM and NPI total score primarily for the low dose group. No significant differences were identified on the other scores. ORM-12741 was generally well tolerated in the study. **CONCLUSIONS:** The study yielded significant positive effects of ORM-12741 on episodic memory in moderate AD patients as add-on therapy over 12 weeks suggesting further study in longer term trials.

Study Supported By: Orion Pharma.

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CSF (1,3) b-D-glucan as an adjunctive test for invasive CNS fungal infection due to presumed Exserohilum rostratum

Jennifer Lyons, MD; Kiran Thakur, MD; Dorlan Kimbrough, MD; Bryan Smith, MD; Farrah Mateen, MD; Kieren Marr, MD; Sean Zhang, MD, PhD; Karen Roos, MD, FAAN

OBJECTIVE: To detail experience with (1,3) b-D-glucan (BG) quantification from cerebrospinal fluid (CSF) as an adjunctive diagnostic test for fungal meningitis during the recent U.S. outbreak. **BACKGROUND:** From May - September 2012, over 14,000 patients who underwent epidural steroid injection were exposed to methylprednisolone acetate from lots contaminated with environmental fungi. Many patients developed serious central nervous system complications, but definitive fungal identification has been elusive. Whereas BG detection in serum can assist in diagnosis of systemic fungal infection, its utility as a CSF assay is unknown. **DESIGN/METHODS:** BG was quantified via Fungitell® assay at Beacon Diagnostic Laboratories (East Falmouth, MA) from CSF of 6 patients who were exposed to the implicated medication but whose fungal cultures and polymerase chain reactions were negative. 4 fit CDC case definitions for probable meningitis. 2 did not fit criteria but underwent lumbar puncture due to exposure history in the setting of clinical illness. **RESULTS:** All 4 probable meningitis cases had detectable CSF BG. One of the cases had two samples separated by 2 weeks during which she was treated and showed symptomatic resolution with voriconazole, and the titer decreased from the first to the second test. Both cases not fitting criteria for probable meningitis had undetectable CSF BG, and clinically their presentations were thought to be due to other causes. **CONCLUSIONS:** Establishing the diagnosis of fungal meningitis in the current nationwide outbreak has been difficult, and little is known about the natural history of this disease or therapeutic responses. Measurement of CSF BG may be a useful adjunctive test for the diagnosis and therapeutic monitoring of fungal meningitis during an outbreak or for culture-negative cases. Additionally, sequential quantification could be useful for determination of therapy duration, but more data would be necessary to understand the anticipated kinetics of antigen positivity and relationship to suspected disease.

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Antipsychotic efficacy and motor tolerability in a Phase III placebo-controlled study of pimavanserin in patients with Parkinson's disease psychosis (ACP-103-020)

Jeffrey Cummings, MD, FAAN; Stuart Isaacson, MD; Roger Mills, MD; Hilde Williams; Kathy Chi-Burris; Daun Bahr; Rohit Dhall, MD; Clive Ballard, MD

OBJECTIVE: A Phase III outpatient study, optimized to reduce placebo response, was conducted to assess the efficacy and safety of pimavanserin in Parkinson's disease psychosis (PDP). **BACKGROUND:** PDP is frequent, distressing and a leading cause of institutionalization. It also complicates PD management and has been linked to increased morbidity, incident dementia and mortality. Current antipsychotics lack efficacy and/or have considerable tolerability and safety concerns. Pimavanserin, a selective non-dopaminergic 5-HT_{2A} receptor antagonist, has shown antipsychotic effects and good tolerability in previous Phase III trials, but a robust placebo effect precluded statistical separation. **DESIGN/METHODS:** Following 2-weeks screening, in which brief (non-pharmacological) psychosocial therapy adapted for PDP (BPST-PD) was offered, 199 non-demented patients with moderate to severe psychosis (and on stable PD medication) were randomized to once-daily oral doses of 40mg pimavanserin or placebo (1:1) for 6 weeks. **RESULTS:** Pimavanserin met the primary endpoint using SAPS-PD (a PD-adapted version of the Scale for Assessment of Positive Symptoms, assessed by independent raters): -5.79 PIM vs -2.73 PBO change from Baseline at Day 43 (LSM difference = -3.06; $p=0.001$). These results were supported by highly significant improvement in the secondary efficacy measure, CGI-Improvement (LSM difference -0.67; $p=0.001$), which was assessed by site investigators blinded to the SAPS-PD. Additionally, clinical benefits were observed in all exploratory efficacy measures with significant improvements in nighttime sleep, daytime wakefulness, and caregiver burden. Consistent with previous studies, pimavanserin met the key secondary endpoint for noninferiority to placebo on motor function (using UPDRS II+III) and was otherwise safe and well tolerated. The most common AEs were UTI (11.7% PBO, 13.5% PIM) and falls (8.5% PBO, 10.6% PIM). The only serious AEs that occurred in more than one patient were UTI (1-PBO, 3-PIM) and psychotic disorder (0-PBO, 2-PIM). **CONCLUSIONS:** These data suggest that pimavanserin is effective, safe and well-tolerated for PDP. Utility in other neuropsychiatric disorders remains to be explored.

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received personal compensation for activities with ACADIA Pharmaceuticals Inc. as an employee. Dr. Dhall has received personal compensation for activities with UCB Pharma and Impax Pharmaceuticals. Dr. Ballard has received personal compensation for activities with Acadia, Lundbeck, Bristol-Myers Squibb, Novartis, and Bial Pharmaceuticals. Dr. Ballard has received research support from Lundbeck and Novo Nordisk.

A phase 2, placebo-controlled, randomized, double-blind trial of tozadenant (SYN-115) in patients with Parkinson's disease with wearing-off fluctuations on levodopa

C. Olanow, MD, FAAN; Robert Hauser, MD, MBA, FAAN; Karl Kieburtz, MD, FAAN; Ann Neale, RN, BSN; Chris Resburg; Uwe Meyya, MD; Stephen Bandak, MB, BS, MRCP

OBJECTIVE: To evaluate the safety and efficacy of tozadenant as an adjunct to levodopa in PD patients with wearing-off fluctuations and determine dosages for phase 3 trials. **BACKGROUND:** Tozadenant is an oral, selective adenosine 2- α receptor antagonist. **DESIGN/METHODS:** This was an international, 12-week, double-blind, phase 2 trial in which patients on stable dosages of levodopa with at least 2.5 hr of OFF time/day were randomized to tozadenant 60, 120, 180 or 240 mg BID, or matching placebo. Primary outcome measure was change from baseline to Week 12 in hr/day spent in the OFF state. A mixed-model repeated-measures ANCOVA was used for analyses with a prespecified hierarchical step-down approach to test multiple dose groups. **RESULTS:** Of 420 patients randomized, 337 completed treatment: mean age, 63.3 yr; PD duration, 8.7 yr; baseline OFF time, ~6 hr. Significant reductions in mean placebo-corrected change from baseline in OFF time were observed with tozadenant (mITT population) 120 mg BID (-1.1 hr, $p=0.0039$) and 180 mg BID (-1.2 hr, $p=0.0039$). ON time with troublesome dyskinesia was not significantly increased in any tozadenant group. Mean placebo-corrected UPDRS III scores significantly improved with tozadenant 120 mg BID (-2.2, $p=0.0325$) and 180 mg BID (-2.5, $p=0.0325$). Mean placebo-corrected UPDRS I-III scores improved significantly in all tozadenant groups (all groups, $p\leq 0.03$) as did mean placebo-corrected CGI-I and CGI-S scores. PGI-I scores significantly improved in the 120 mg BID group. Most common AEs in the combined tozadenant groups were dyskinesia, nausea, dizziness, constipation, PD worsening, insomnia, and falls. **CONCLUSIONS:** Tozadenant, at a daily dosage of 120 or 180 mg BID, was generally well tolerated and demonstrated efficacy in reducing OFF time and improving motor signs without significantly increasing troublesome dyskinesia. These two dosages can be considered for future trials.

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A placebo controlled, randomized, double-blind study to assess the safety and clinical benefit of rasagiline as an add-on therapy to dopamine agonist monotherapy in early Parkinson's disease (PD): The ANDANTE study

Robert Hauser, MD, MBA, FAAN; Dee Silver, MD; Azhar Choudhry, MD; Stuart Isaacson, MD

OBJECTIVE: Determine the efficacy and safety of rasagiline add-on therapy for early-PD patients sub-optimally controlled by dopamine agonist (DA) monotherapy. **BACKGROUND:** DAs are often used as initial symptomatic therapy for early-PD. With disease progression, DA monotherapy can become suboptimal, requiring increasing dose to maintain efficacy. However, increasing DA dose is associated with a higher risk of Adverse Events (AEs) (Antonini et al PMID:19709931). Rasagiline is a selective, irreversible MAO-B inhibitor that reduces striatal dopamine catabolism, and this distinct mode of action provides a rationale for add-on therapy to DAs for additional symptomatic benefit. **DESIGN/METHODS:** ANDANTE is a Phase-IV, 18-week study of PD patients (Hoehn & Yahr 1-3) aged ≥ 30 years taking stable DA dosages of ≥ 6 mg/day ropinirole or ≥ 1.0 mg/day pramipexole with suboptimal symptom control. Patients were randomized to rasagiline 1mg or placebo; DA dosage remained stable throughout. Primary outcome: change from baseline in total-UPDRS score. Secondary outcomes: changes from baseline in UPDRS activities of daily living (ADL) and motor scores, and CGI-I. Safety was assessed by AE frequency and severity, and discontinuation due to AEs. 328 patients were randomized, and 321 patients (mean age 62.6; duration PD 2.13 years) were included in the efficacy analysis. **RESULTS:** Treatment with add-on rasagiline resulted in a significant improvement in total-UPDRS score vs. placebo (Primary endpoint: treatment effect $\pm$ SE -2.4 $\pm$ 0.95 (95% CI -4.3,-0.5, $p=0.012$). Rasagiline also significantly improved UPDRS-motor scores ($p=0.007$). There were no significant differences between groups for UPDRS-ADL ($p=0.301$) or CGI-I scores. Rasagiline was well-tolerated, with no significant difference in percentage of patients with AEs (64.2% vs. 61.0%) or serious AEs (4.9% vs. 3.0%) vs. placebo. Only 11 patients required rescue with levodopa during the study. **CONCLUSIONS:** Addition of rasagiline significantly improved motor symptoms in patients sub-

optimally controlled with DA monotherapy, and was safe and well-tolerated with an AE profile similar to placebo.

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Davunetide for progressive supranuclear palsy: Results of the AL-108-231, phase 2/3, 52 week, multi-center, randomized, double-blind, placebo-controlled clinical trial

Adam Boxer, MD, PhD; Anthony Lang, MD, FAAN; Murray Grossman, MD, FAAN; David Knopman, MD, FAAN; Bruce Miller, MD, FAAN; Lon Schneider, MD; Rachelle Doody, MD, PhD, FAAN; Andrew Lees, MD, FRCP; Joe Hirman; Bruce Morimoto; Michael Gold, MD

OBJECTIVE: To evaluate the efficacy and safety of davunetide for the treatment of PSP. **BACKGROUND:** Davunetide (AL-108) is an 8 amino acid peptide that promotes microtubule stability, decreases tau phosphorylation and improves memory in pre-clinical studies. Since PSP is tightly linked to tau pathology, we hypothesized that davunetide would be an effective treatment for PSP. **DESIGN/METHODS:** A double-blind, parallel group, clinical trial of davunetide 30 mg or matched placebo (randomized 1:1) administered intranasally twice daily for 52 weeks was conducted at 47 centers in North America, Europe and Australia. Participants were required to meet NINDS-SPSP criteria for possible or probable PSP, and were allowed to remain on stable doses of levodopa or coenzyme Q10. Co-primary outcomes were the PSP Rating Scale (PSPRS) and Schwab and England ADL (SEADL) scale. Safety was assessed by adverse events (AEs) and routine laboratory tests. Secondary outcomes included the Clinical Global Impression of Change (CGIC) and the change in brain atrophy on MRI. **RESULTS:** 360 participants were screened, 313 were randomized and 243 (77.6%) completed the study. Baseline demographics and disease severity were similar between treatment groups. Mean age was 68 ± 6.6 , baseline PSPRS score was 40 ± 11 and 94.2% (of 244 with available data) had the H1/H1 tau haplotype. There were no differences between davunetide and placebo-treated groups at 52 weeks in the PSPRS ($p=0.41$) or SEADL ($p=0.92$) scores. Mean PSPRS change was approximately 11 ± 9 overall. There were also no group differences in CGIC scores ($p=0.26$) or MRI ventricular volumes ($p=0.77$; $n=215$). There were 10 deaths in the davunetide group and 8 in the placebo group, with 54 serious AEs in each. Nasal AEs were more frequent in the davunetide group. **CONCLUSIONS:** Davunetide is not an effective treatment for PSP. PSP clinical trials are feasible and should be pursued with other promising tau-directed therapies.

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Interim analysis of 12 patients with amyotrophic lateral sclerosis (ALS) treated with autologous differentiated mesenchymal stem cells: Preliminary data of a Phase I/II clinical trial

Dimitrios Karussis, MD, PhD; Panayiota Petrou; Daniel Offen; Marc Gotkine, MD; Zohar Argov, MD; Adi Vaknin-Dembinsky, MD; Ibrahim Kassis; Tamir Ben-Hur, MD, PhD; Eldad Melamed, MD

OBJECTIVE: To evaluate the safety and tolerability of treatment with autologous mesenchymal stem cells differentiated to secrete neurotrophic factors (MSC-NTF) in ALS patients utilizing the intramuscular(IM) and the intrathecal(IT) way of administration. **BACKGROUND:** A previous study from our group at Hadassah has shown the safety of IV/IT administration of unmodified MSC in ALS patients. MSC-NTF demonstrated neuroprotective effects in various animal models of neurodegenerative diseases, including ALS. **DESIGN/METHODS:** This Phase I/II clinical study will include upon completion 24 ALS patients. Twelve participants have already been recruited. MSC were isolated from the patients' own bone marrow, expanded ex-vivo and induced to differentiate into MSC-NTF secreting GDNF and BDNF. Autologous MSC-NTF cells were transplanted, by IM (at 24 sites:200,000 cells per site) or IT (1×10^6 cells/

kg) injections to patients with early (ALSFRS score of >30; n=6) or advanced ALS (ALSFRS: 15-30; n=6), respectively. Patients were followed up clinically on a monthly basis for a pre-treatment period of 3 months and for 6 months post-transplantation. Respiratory function tests, 3D-MRI of the muscles and compound muscle action potential amplitudes at 3 sites were used as additional surrogate markers of disease activity. **RESULTS:** During the six-month follow-up of the transplanted patients, no serious treatment-related adverse events were observed, indicating a short-term treatment safety. The clinical follow-up of the patients revealed initial indications of beneficial clinical effects in the MSC-NTF transplanted patients, as evidenced by a significant change in the rate of clinical progression (ALSFRS), in the respiratory function, in electrophysiology and in the 3D-MRI volumetric evaluation of the muscles, as compared to the 3 months preceding the treatment. **CONCLUSIONS:** Preliminary results of our ALS trial with autologous IM/IT MSC-NTF transplantation indicate that the used treatment protocols appear to be safe. Further analysis of the accumulated data and longer follow up of the participating patients are needed to confirm these observations.

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A Study to Evaluate Efficacy, Safety and Tolerability of Single Doses of Tirasemtiv in Patients with Myasthenia Gravis

Donald Sanders, MD, FAAN; Jeffrey Rosenfeld, PhD, MD, FAAN; Mazen Dimachkie, MD, FAAN; Lisa Meng; Fady Malik; Tirasemtiv in Myasthenia Gravis Study Group

OBJECTIVE: To determine the effect of single doses of tirasemtiv on measures of skeletal muscle function and fatigability in patients with generalized MG. **BACKGROUND:** Tirasemtiv (formerly CK-2017357) is a fast skeletal troponin activator that sensitizes the sarcomere to calcium, thus increasing muscle force following sub-maximal neuronal input and reducing fatigability. In an animal model of myasthenia gravis (MG), single doses of tirasemtiv improved muscle force and reduced fatigability in situ while increasing grip strength (Nat Med. 2012 Feb 19;18(3):452-5). **DESIGN/METHODS:** 32 patients with AChR-antibody positive MG and muscle weakness were recruited. In a double-blind random treatment sequence, each patient received single doses of tirasemtiv 250 mg, tirasemtiv 500 mg, and placebo; each dose was separated by at least one week. Outcome measures included the Quantitative MG Score (QMG), MG Composite (MGC) and Manual Muscle Testing, Modified MG Symptom Score, and Global Assessment by patient and investigator. **RESULTS:** Six hours after dosing, improvements in the QMG were statistically significant and related to the tirasemtiv dose (-0.49 QMG points per 250 mg; p = 0.02). Also at six hours after dosing, increases in the percent predicted forced vital capacity were statistically significantly related to the dose level (2.2% per 250 mg; p = 0.04), as were the individual comparisons of each tirasemtiv dose level versus placebo. QMG score improved at least 3 points in twice as many patients after 500 mg than after placebo (p=0.098). Both doses of tirasemtiv were well-tolerated; there were no premature terminations or serious adverse events. The most commonly reported adverse event was dizziness, which was mild in all but one case, which was classified as moderate. **CONCLUSIONS:** The results of this study suggest that tirasemtiv may improve function in MG and will be used to support further development of tirasemtiv in neuromuscular diseases.

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Droxidopa Treatment Impact on Orthostatic Symptoms and Standing Systolic Blood Pressure in Patients with Parkinson's Disease (PD) and Symptomatic Neurogenic Orthostatic Hypotension (NOH)

Stuart Isaacson, MD; Robert Hauser, MD, MBA, FAAN; Cameron Szakacs, PhD; Christopher Cioffi, PhD

OBJECTIVE: Evaluate clinical efficacy and safety of droxidopa as demonstrated by changes in Orthostatic Hypotension Questionnaire (OHQ), dizziness/lightheadedness (Orthostatic Hypotension Symptom Assessment Item 1), standing systolic blood pressure (SBP), and falls. **BACKGROUND:** Autonomic dysfunction is common in PD. Approximately 18% of patients with PD develop symptomatic NOH.¹ NOH results from failure of the autonomic nervous system to respond to changes in posture due to an inadequate release of norepinephrine (NE).² Droxidopa is an oral pro-drug converted to NE. **DESIGN/METHODS:** Patients were randomized to placebo or droxidopa (Study 306); dose titrated to 100-600mg TID over a 2-week double-blind period, followed by 8 weeks of double-blind treatment. Change in dizziness/lightheadedness from baseline to Week 1 was the primary efficacy measure. Secondary outcome measures included change in OHQ, standing SBP, and falls. Study 306 was separated into two parts following an interim analysis; 306A (n=51) and 306B (n=174). Meta-analyses were performed to evaluate efficacy and safety of all patients (n=225, mITT: n=197). **RESULTS:** Droxidopa patients experienced significant improvement in dizziness/lightheadedness at Week 1 compared to placebo (1.2 unit difference; p=0.008), and showed a trend toward improvement at Week 8 (0.8 unit difference; p=0.077). Standing SBP significantly improved with droxidopa compared to placebo at

Week 1 (6.8 mmHg; p=0.014), and showed a numerical improvement at Week 8 (2.2 mmHg; p=0.414). Droxidopa also improved symptoms and symptom impact compared to placebo as evaluated by OHQ. Droxidopa patients experienced a rate of falls/patient/week of 0.38 vs. 1.73 for those on placebo, a 78% reduction (p=NS). The most common (> 5%) adverse events associated with droxidopa treatment included headache, dizziness, hypertension, nausea, and fatigue. **CONCLUSION:** Droxidopa treatment improved signs and symptoms of NOH associated with PD, including dizziness/lightheadedness and standing SBP. Droxidopa was safe and well tolerated. 1. Ha et al. Parkinsonism Relat Disord.2001; 17:625-8. 2. Freeman R. N Engl J Med.2008;358:615-24.

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IMS-III Like Subgroup Analysis in the North American SOLITAIRE Stent-Retriever Acute Stroke Registry

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OBJECTIVE: To present the clinical and angiographic outcomes of IV-rPA plus thrombectomy using a newer generation device from the North American SOLITAIRE-FR Stent-Retriever Acute Stroke (NASA) Registry. **BACKGROUND:** IMS-III demonstrated no significant difference between treatment with IV-rPA alone or IV-rPA plus IA therapy. However, the trial included only earlier generations of thrombectomy devices and did not evaluate the efficacy of newer devices. **DESIGN/METHODS:** The investigator-initiated NASA Registry recruited sites within North America to submit data on consecutive patients treated with Solitaire-FR. A cohort similar to the IMS-III IV-rPA+Solitaire-FR population was identified and compared to those receiving Solitaire-FR alone. sICH was defined as any parenchymal hematoma, SAH, or IVH associated with a worsening of the NIHSS score by 4 or more within 24 hours. Successful recanalization was defined as TIMI ≥2. Good clinical outcome was defined as a 90-day mRS ≤2. **RESULTS:** 334 patients underwent treatment using the SOLITAIRE-FR device in 23 centers. Mean age was 67.3±15.1 years; mean NIHSS was 18 (IQR 14-23). Of those, 44% (147/333) were treated with IV-rPA+Solitaire-FR versus 56% (186/333) with Solitaire-FR alone. Recanalization rate was 86.4% (127/147) in the IV-rPA+Solitaire-FR versus 82.3% (153/186) in the SOLITAIRE-FR only group (p=0.4). sICH was noted in 11% (16/146) of IV-rPA+Solitaire-FR patients compared to 9.2% (17/185) in the Solitaire-FR group (p=0.7). In IV-rPA+Solitaire-FR patients with available outcomes, 52% (66/127) had achieved a 90-day good clinical outcome versus 35.6% (57/160) of patients treated with Solitaire-FR alone (p=0.006). Mortality was 25% (33/132) in the IV-rPA+Solitaire-FR versus 35.4% (58/164) in Solitaire-FR alone groups (p=0.06). **CONCLUSIONS:** In the NASA registry, the IMS-III like group (IV-rPA+Solitaire-FR) demonstrated a higher rate of good clinical outcome versus treatment with Solitaire alone and a trend towards reduced mortality.

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Mutations in DEPDC5 cause Familial Focal Epilepsy with Variable Foci and are a common cause of familial non-lesional focal epilepsy

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Cossette, MD; Paul Thomas; Jozef Gecz; Jose Serratos, MD, PhD; Oebele Brouwer; Frederick Andermann, MD, FRCP, FAAN; Eva Andermann, MD, PhD; Arn van den Maagdenberg; Samuel Berkovic, MD, FRACP; Ingrid Scheffer

OBJECTIVE: To identify the genetic cause of autosomal dominant Familial Focal Epilepsy with Variable Foci (FFEVF), to investigate the prevalence of mutations in the FFEVF causative gene in familial cases of non-lesional focal epilepsy, to study the expression in the brain and the subcellular localization of the encoded protein. **BACKGROUND:** FFEVF is characterized by seizures arising from different cortical regions in different affected family members. Brain imaging is normal. Seizure onset varies from infancy to adult life. Affected individuals occasionally have neuropsychiatric co-morbidities. Linkage studies mapped FFEVF to chromosome 22q12, but the causative gene had so far eluded identification. **DESIGN/METHODS:** We applied exome sequencing to two FFEVF families previously linked to chromosome 22q12, identifying *DEPDC5* as the most likely candidate gene. We sequenced *DEPDC5* in six additional 22q12-linked families and scanned *DEPDC5* for sequence variation in 82 unrelated probands from families with at least two individuals with non-lesional focal epilepsy. We used qRT-PCR, immunofluorescence and western blot analysis to study *DEPDC5* expression and subcellular localization. **RESULTS:** Heterozygous mutations in *DEPDC5* were identified in 7/8 FFEVF families linked to chromosome 22q12 and in 10/82 (12.2%) probands from the small families with focal epilepsy. Each *DEPDC5* mutation segregated with the FFEVF phenotype in the respective family and was absent in both dbSNP135 and an in-house exome sequencing database of 710 chromosomes. Most mutations caused premature termination codons suggesting haploinsufficiency as pathogenic mechanism. *DEPDC5* encodes a 1604 amino acid protein of unknown function, probably implicated in modulation of intracellular signaling. Mouse *Depdc5* transcripts were detected at low levels in all brain regions and throughout brain development. Immunofluorescence analyses in mouse and human brain showed specific expression in neurons and perinuclear localization. **CONCLUSIONS:** Our findings establish *DEPDC5* mutations as the most common known cause of familial focal epilepsy and identify a novel pathogenic pathway for epilepsy.

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A Multicentre, Randomised, Open-Label, Comparative Phase 4 Trial to Assess Changes in Dementia Diagnostic Category and Diagnostic Confidence after DaTscan Imaging in Subjects with an Uncertain Diagnosis of Dementia with Lewy Bodies (Possible DLB)

Zuzana Walker; Alessandro Padovani, MD; Alan Thomas; Fraser Inglis; Naji Tabet; Michael Rainer; Gilberto Pizzolato, MD; Emilio Moreno-Carretero

OBJECTIVE: To evaluate the impact of DaTscan™ SPECT imaging on dementia diagnostic category and on the diagnostic confidence of clinicians in patients with a diagnosis of possible DLB. **BACKGROUND:** A clinical diagnosis of Dementia with Lewy bodies (DLB) has good specificity but low sensitivity and is particularly challenging in patients with an uncertain diagnosis (possible DLB). DaTscan™ (Ioflupane ¹²³I) is a radiopharmaceutical for single-photon emission computed tomography (SPECT) brain imaging to visualize the dopamine transporter receptors located on the presynaptic terminals of dopaminergic neurons. **DESIGNS/METHODS:** One hundred and eighty seven patients with a diagnosis of possible DLB were recruited from 23 centers in 6 European countries. Patients were randomized to have a DaTscan™ at baseline (127 patients; imaging group) or to have no-imaging (60 patients; control group). The proportion of patients with changes in clinical diagnosis (to probable DLB or non-DLB) and changes in the confidence in diagnosis from baseline was compared between the two groups at 8 and 24 weeks of follow-up. **RESULTS:** Significantly more patients in the DaTscan™ imaging group had a change in diagnostic category after 8 weeks (62% vs 4%; $P < .0001$) and after 24 weeks (69% vs 16%; $P < .0001$) compared to patients in the control group. Additionally, significantly more patients in the imaging group were given more confident diagnoses at 8 and 24 weeks of follow-up ($P < .0001$) compared to the control group. Clinicians were more likely to change the diagnostic category if the DaTscan™ was abnormal (82%) than if the result was normal (48%). **CONCLUSIONS:** DaTscan™ SPECT imaging significantly contributed to change diagnostic category and improve diagnostic confidence, proving to be a useful adjunct in the diagnosis of dementia in patients with possible DLB. Changes in diagnostic category were less frequent in the control group despite a six-month prospective follow-up.

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Neocortical ictal high frequency oscillations (HFO) are a surrogate marker of increased action potential firing rate and synchrony that discriminate the ictal focus from the penumbra

Shennan Weiss, MD; Garrett Banks; Guy McKhann, MD; Robert Goodman; Ronald Emerson, MD, FAAN; Catherine Schevon, MD; Andrew Trevelyan

OBJECTIVE: To identify the cellular electrophysiological correlates of ictal high frequency oscillations in an effort to better identify the active seizure focus. **BACKGROUND:** Traditionally, the epileptogenic zone is characterized by the earliest and largest amplitude aberrant EEG activity in the 1-50 Hz spectrum correlated with a clinical event. However, large EEG signals may arise from either focal discharges or from large inhibitory synaptic currents present in surrounding territories which have not been incorporated into the seizure, and where neural firing is unstructured. Conventional EEG interpretation, therefore, cannot generally distinguish the core active regions from the surrounding territory. To overcome this ambiguity, we sought to test late-onset, sustained ictal high frequency oscillations (HFOs) as surrogate markers of ictal discharges in the underlying cortex. **DESIGNS/METHODS:** Four patients with neocortical epilepsy were implanted with a 96 channel micro-electrode array in or near the seizure onset zone. Simultaneous recordings were also performed using standard grids and strips of surface macroelectrodes to determine the seizure onset zone. We recorded ten seizures with video correlation and analyzed multi-unit (neuron) activity, high frequency oscillations, and standard EEG. **RESULTS:** We demonstrate that sustained, repetitive ictal HFOs detectable on the cortical surface by electrocorticography correlate well with the intense, hyper-synchronized neuronal population firing bursts that are present in territories recruited into the seizure. Sustained HFOs are not present in penumbral areas where such bursting is notably absent. **CONCLUSIONS:** We conclude that ictal HFOs detected on the cortical surface are indicative of increased neuronal activation in the underlying cortex and can distinguish cortical regions recruited into a seizure from the penumbra.

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Reduced $\Delta 5$ -ADIOL in CSF and Plasma as a Biomarker of Neurocognitive Impairment in HIV Infection

Kaoru Saijo, MD, PhD; David J. Moore, MD; Ben Gouaux; Igor Grant, MD; Ronald Ellis, MD, PhD

OBJECTIVE: To determine whether plasma and CSF levels of $\Delta 5$ -ADIOL are reduced in HIV+ with NCI. **BACKGROUND:** Microglial activation and related inflammatory responses have been demonstrated in HIV-associated neurocognitive impairment (NCI) and may play a role in neuropathogenesis, even after combination antiretroviral therapies (cART) produce successful viral suppression and immune recovery. We evaluated a recently discovered pathway by which microglial inflammatory responses are downregulated, through binding of the endogenous neurosteroid 5-ANDROSTEN-3 β , 17 β -DIOL ($\Delta 5$ -ADIOL) to the estrogen receptor (ER) β . **DESIGNS/METHODS:** Participants: 10 HIV+ (5 with NCI); 5 healthy, HIV seronegative (HIV-) controls matched by gender (100% men), age (mean, 42.2) and education (mean 12.5). All HIV+ were receiving cART and virologically suppressed. Participants underwent lumbar puncture, phlebotomy and detailed medical, neurological and neurocognitive examinations. Neurosteroids were extracted from cerebrospinal fluid (CSF) and plasma and quantitated by enzyme immunoassay (EIA). **RESULTS:** Levels of ADIOL in CSF were on average 6-fold higher than in plasma. Compared to HIV- individuals (CSF, 1289.7 $\pm$ 374.6; plasma, 215.4 $\pm$ 263.1) and to HIV+ unimpaired subjects (CSF, 1010.7 $\pm$ 450.3; plasma, 38.9 $\pm$ 44.3) CSF ADIOL was decreased in impaired HIV+ subjects both in CSF (507.2 $\pm$ 188.1, $p < 0.01$) and plasma (5.9 $\pm$ 4.3). **CONCLUSIONS:** CSF $\Delta 5$ -ADIOL levels were reduced in HIV+ NCI participants. Since the expression of HSD17B14 is down-regulated by inflammation and up-regulated by the anti-inflammatory cytokine interleukin, (IL)-10, $\Delta 5$ -ADIOL levels in CSF might be used as a biomarker for neuroinflammation in HIV. If confirmed, these results open the possibility of preclinical and clinical studies on exogenous ER beta ligands as potential interventions for HIV NCI.

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The role of stabilized neuropeptides derived from hyperimmune caprine sera (HICS) in motor neuron disease - implications for a novel therapeutic strategy

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OBJECTIVE: To determine if targeting the HPA axis at a specific site using novel stabilized neuropeptides could elicit efficacy in the G93A SOD1 murine model and in patients from a multi-center open-label prospective ALS study conducted up to 12 months in duration. **BACKGROUND:** HICS has been demonstrated recently to have neuroprotective and neuroregenerative properties in several CNS in-vivo animal models and in a human phase II double-blind placebo cross-over clinical trial in secondary progressive multiple sclerosis. **DESIGNS/METHODS:** A. Age-matched G93A male/female mice $n=20$ per treatment group (naïve/WT, naïve/SOD1 and HICS/SOD1) animals were treated daily (100mcg s.c.) from day 60 to 150 and analyzed using standard methods of assessment including 1H-MRS. B. A single-arm multi-center open-label study up to 12 months was conducted in 21 subjects with definite ALS receiving a daily s.c. dose of 1ml (4.5mg/ml) of HICS. The primary intention-to treat analyses were ALSFRS-R and survival. Secondary outcomes were ALSAQ-40, Jablecki score, FVC, muscle strength, BMI, safety and tolerability. **RESULTS:** A. Significant maintenance was observed in rotarod latency, grip strength and concomitant changes observed in several key cellular metabolites using 1H-MRS at 90 and 110 days. Delayed onset of disease and prolonged survival were also observed though not significant. B. In summary, no fall in the ALSFRS-R was noted in patients, with the majority having been treated for >6 months, patients showed a significant improvement in ALSFRS-R (7.8%, $p<0.05$), ALSAQ-40 (15%, $p<0.05$), a significant improvement in ALS scores of Jablecki (11.4%, $p<0.05$), muscle power and lung function during the study period were also noted. No adverse events were recorded during the entire duration of the study using HICS. **CONCLUSIONS:** HICS showed efficacy in the G93A SOD1 mouse and in humans with ALS with no adverse event recorded. The latter confirmed the safety profile of the drug in two separate phase II clinical trials recently completed.

Study Supported By: Daval International Ltd.

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¹H MRS Reveals Decreased Motor Cortex Glutathione in Patients with ALS

Nora Weiduschat; Xiangling Mao; Jonathan Hupf; Nicole Armstrong; Dale Lange, MD, FAAN; Hiroshi Mitsumoto, MD, FAAN; Dikoma Shungu, PhD

OBJECTIVE: To compare in vivo levels of glutathione (GSH) as measured by magnetic resonance spectroscopy (MRS) in the motor cortex of ALS patients with those in healthy volunteers (HV). **BACKGROUND:** Oxidative stress has been implicated in both sporadic and familial forms of amyotrophic lateral sclerosis (ALS). While glutathione levels have been associated with survival and cell pathology in preclinical ALS models, direct in vivo evidence of GSH deficiency in patients' brain is lacking. **DESIGNS/METHODS:** This cross-sectional observational study enrolled 12 ALS patients, diagnosed according to El Escorial criteria, and 11 age-matched HV. In vivo brain GSH spectra were recorded from a single 20x25x25mm³ precentral gyrus voxel in the clinically most affected hemisphere on a 3.0 T GE MR system, using the standard J-edited spin echo difference method and an 8-channel phased-array head coil as described previously (Shungu 2012). GSH peak areas were derived by frequency-domain spectral fitting and expressed as ratios relative to the area of simultaneously acquired unsuppressed voxel tissue water (W). N-acetylaspartate (NAA), lactate, GABA and glutamate were obtained from the same voxel. **RESULTS:** Motor cortex GSH/W was decreased in the ALS group (Mean=0.0013, SD 0.0004) compared to HV (Mean=0.0016, SD 0.0004) ($p=.021$). Also NAA/Cr was decreased ($p=.013$) in ALS patients (Mean=2.03, SD 0.17) compared to HV (Mean=2.24, SD 0.19). There were no significant differences between the groups for any other metabolite or age. Age had no significant effect on GSH/W or NAA/Cr in our sample. **CONCLUSIONS:** To our knowledge, this is the first study to show decreased cortical GSH in vivo in ALS, directly implicating oxidative stress. Our finding of decreased NAA/Cr in ALS is consistent with prior MRS studies and suggests neurodegeneration. Further studies are warranted to investigate MRS measurement of GSH as potential noninvasive biomarker for diagnosis and therapy monitoring. Shungu et al. NMR Biomed. 2012 Sep;25(9):1073-87.

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Evidence of primary vascular injury after acute head trauma in the Traumatic Head Injury Neuroimaging Classification (THINC) Study

Gunjan Parikh, MD; Abhik Ray-Chaudhury, MD; Lawrence Latour

OBJECTIVE: To identify the neuroimaging correlates of these two pathological entities in hyperacute mild traumatic brain injury (mTBI). **BACKGROUND:** Pathological studies following severe head trauma reveal small hemorrhagic lesions of two types: punctate lesions within the corpus callosum, grey-white junction, or brainstem are associated with diffuse axonal injury (DAI) while "streak-like" lesions in the parasagittal white matter track penetrating vasculature. **DESIGN/METHODS:** This is a prospective study of acute TBI in the ED with evidence of blood on a clinical CT or research MRI. Focal lesions on T2* MRI were classified as i) microbleeds (punctate) or ii) linear lesions (tube-shaped, branching, multiple axial slices) and were graded for severity. Lesions were classified according to location, ischemia on DWI, edema on FLAIR, and focal findings on 3DT1. Concordance and discordance on CT was noted. Fisher exact was used. **RESULTS:** Of 256 studied over 24 months, 104

(41%) had imaging evidence of hemorrhage, with 78% male, median age was 50, 91% had arrival GCS 13-15, 67% reported loss of consciousness, 65% reported amnesia, and 39% had a negative CT. Median time injury to MRI was 17 hours. Of the 104, 21 (20%) had microbleeds while 34 (33%) had linear lesions. Microbleeds were distributed throughout the brain (lobar=37; deep=3; infratentorial=9), whereas linear lesions were found primarily in the anterior corona radiata ($n=28$; 82%). 20 (59%) linear lesions traversed white matter, gray matter, and sulcus on 3DT1. 23 (68%) were graded as "severe". Ischemia on DWI or edema on FLAIR was association with linear lesions, $p=0.001$. **CONCLUSIONS:** Linear hemorrhagic lesions following mTBI are distinct from punctate microbleeds and may be the imaging correlate of vascular injury seen in histopathology following severe TBI. While these lesions are often equated to DAI, the MRI findings are suggestive of primary injury to the vasculature, and thus may be a target for acute therapy.

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Natalizumab-associated progressive multifocal leukoencephalopathy (PML) in multiple sclerosis patients: Survival and functional outcome when asymptomatic at diagnosis

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OBJECTIVE: To evaluate outcomes in natalizumab-treated multiple sclerosis (MS) patients who were asymptomatic when diagnosed with PML. **BACKGROUND:** As of January 1, 2013, 319 natalizumab-associated PML cases were confirmed in MS patients. **DESIGNS/METHODS:** Asymptomatic patients, diagnosed by MRI findings consistent with PML and JCV DNA positive CSF, were compared with patients symptomatic for PML at diagnosis. Demographics, MRI, and survival were analyzed. Expanded Disability Status Scale (EDSS) and Karnofsky Performance Scale (KPS) scores were recorded pre-PML, at diagnosis, and at 6 and 12 months post-PML diagnosis. Data are as of January 1, 2013. **RESULTS:** At diagnosis, 21 PML patients (mean age 45.1 years; 66.7% female; median natalizumab exposure 36 doses) were asymptomatic (AP); 298 (mean age 45.8 years; 70.5% female; median natalizumab exposure 38 doses) were symptomatic (SP). PML lesions on MRI in AP vs SP were 76% vs 36% unilobar, 14% vs 25% multilobar, and 10% vs 39% widespread, respectively. In both AP and SP, frontal lesions predominated. Symptoms developed in 10/21 AP at 13.8 weeks (mean) after diagnosis of PML; 5 of these patients had cognitive deficits and/or behavioral changes. Mean EDSS and KPS scores for AP vs SP, respectively, were as follows: pre-PML, EDSS 3.2 ($n=14$) vs 3.8 ($n=145$; $P=0.263$), KPS 88.0 ($n=5$) vs 80.1 ($n=72$; $P=0.144$); at diagnosis, EDSS 3.6 ($n=8$) vs 5.3 ($n=154$; $P=0.020$), KPS 66.7 ($n=6$) vs 53.6 ($n=88$; $P=0.129$); at 6 months, EDSS 4.7 ($n=9$) vs 6.9 ($n=70$; $P=0.003$), KPS 71.7 ($n=9$) vs 46.0 ($n=88$; $P<0.001$); at 12 months, EDSS 3.7 ($n=3$) vs 6.5 ($n=39$; $P=0.066$), KPS 70.0 ($n=4$) vs 46.9 ($n=50$; $P=0.021$). As of January 1, 2013, 100% of AP and 76.5% of SP have survived. **CONCLUSIONS:** Preliminary data suggest that PML patients who are asymptomatic at diagnosis may have improved survival and less functional disability compared with PML patients who are diagnosed when symptomatic.

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Pilot study of monthly pulse adrenocorticotrophic hormone (ACTH) or methylprednisolone as an add-on therapy to beta-interferons for long-term treatment of multiple sclerosis

Regina Berkovich, MD, PhD; Lilijana Amezcu, MD; Dawood Subhani, MBBS; Steven Cen, PhD

OBJECTIVE: This single-center, examiner-blinded pilot study evaluated the efficacy and safety of pulse adrenocorticotrophic hormone (ACTH) treatment added to beta-interferon in breakthrough multiple sclerosis (MS) compared with pulse methylprednisolone (MP). **BACKGROUND:** ACTH may have immune-modulating mechanisms beyond steroidogenesis that are relevant to the MS disease course. Although ACTH gel is approved to treat MS relapses, its use as pulse therapy is less known. **DESIGNS/METHODS:** MS patients receiving ongoing beta-interferon treatment were eligible if they had Expanded Disability Status Scale (EDSS) scores of 3.0-6.5 and ≥ 1 relapse or new T2 or Gadolinium-enhanced lesion within the previous year. Patients were randomly assigned to open-label ACTH (80 units IM once/day x 3 consecutive days) or MP (1 gram IV x 1 dose) monthly for 12 months, with assessments every 3 months for 15 months. Outcomes included relapse rate (primary), EDSS, MS Functional Composite, and MS Quality of Life. **RESULTS:** The study included 23 patients (ACTH: $n=12$, mean $\pm$ SD EDSS 4.6 ± 1.5 ; MP: $n=11$, mean $\pm$ SD EDSS 4.6 ± 1.3). Over 15 months, the cumulative number of relapses/patient was 0.08 (95% CI: 0.01-0.54) with ACTH and 0.80 (95% CI: 0.36-1.75) with MP (risk ratio [MP vs ACTH]: 9.56 [95% CI: 1.23-74.6; $P=0.03$]). The cumulative number of psychiatric episodes/patient was greater with MP (0.55 [95% CI: 0.12-2.6]) than with ACTH (0 episodes; $P<0.0001$). The urinary tract infection cumulative incidence rate with MP was 0.65/patient and with ACTH was 0.16/patient ($P=0.25$). Mixed effect modeling showed no difference between groups in trajectory slopes of EDSS over time, but significantly stronger ($P=0.03$) improvement in Mental Health Inventory for ACTH (slope: 0.95/month [$P=0.02$]) compared with MP (slope: 0.29/month [$P=0.32$]). **CONCLUSIONS:** These data suggest a potential benefit of ACTH pulse therapy

in breakthrough MS with more favorable relapse and psychiatric side effect profiles. Further studies, including randomized controlled trials are needed to validate these findings.

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Percutaneous Transluminal Venous Angioplasty (PTVA) is Ineffective in Correcting Chronic Cerebrospinal Venous Insufficiency (CCSVI) and May Increase Multiple Sclerosis (MS) Disease Activity in the Short Term: Safety and Efficacy Results of the 6-Month, Double-Blinded, Sham-Controlled, Prospective, Randomized Endovascular Therapy in MS (PREMiSe) trial

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OBJECTIVE: To investigate the safety and efficacy of percutaneous transluminal venous angioplasty (PTVA) for correcting chronic cerebrospinal venous insufficiency (CCSVI) in multiple sclerosis (MS). **BACKGROUND:** The safety and efficacy of PTVA for correcting CCSVI was not tested in randomized, double-blinded, sham-controlled studies. **DESIGN/METHODS:** The trial was planned in two phases. Phase I was an open-label safety 6-month follow-up study that included 10 MS patients, whereas phase II, initiated after completion of phase I, was a randomized, double-blinded, sham-controlled PTVA intervention, 6-month follow-up study that included 19 patients (10 in the sham and 9 in the treated arm). Qualification on non-invasive (≥ 2 Doppler sonography criteria) and invasive ($\geq 50\%$ lumen reduction on catheter venography in the azygous or internal jugular veins) screening assessments was needed for study participation. All patients were assessed at 1, 3 and 6 months post-PTVA with MRI, clinical and Doppler sonography. The primary endpoints were safety at 24 hours and 1 month, venous outflow restoration ($>75\%$ compared to baseline), and the effect of PTVA on new lesion activity and relapse rate over 6 months. Secondary endpoints included changes in disability and MRI brain volume. Neuropsychological and quality of life outcomes were considered tertiary endpoints. **RESULTS:** No intra- or post-operative complications occurred during the study. Venous outflow restoration of $>75\%$ compared to baseline, was achieved only in phase I at 1 month,

but not in phase II. In phase II, higher MRI [cumulative number of new contrast enhancing (19 vs. 3, $p=0.062$) and new T2 lesions (17 vs. 3, $p=0.066$)] and relapse activity (4 vs. 1, $p=0.389$) were identified in the treated vs. the sham arm over 6 months. No differences in secondary or tertiary endpoints between phase II groups were detected. **CONCLUSIONS:** PTVA was ineffective in correcting CCSVI and may increase MS disease activity in the short-term.

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