2019 Emerging Science Program Schedule

Following is the schedule of Emerging Science abstracts to be presented at the 2019 AAN Annual Meeting. Abstracts qualify for Emerging Science presentations by having key aspects of research conducted after the October 22 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 so we are excited to announce that there will be 11 abstracts presented as part of the Emerging Science program. 11 dual presentation abstracts will be featured in data blitz format during the first 35 minutes of the Emerging Science Platform session on Tuesday, May 7 from 11:45 a.m. to 12:20 p.m., followed by poster presentations in the same room from 12:20 p.m. to 12:45 p.m. One abstract will be presented during the Clinical Trials Plenary session.

The 2019 Emerging Science abstracts are embargoed until 12:01 a.m. Eastern Standard Time on Friday, May 3.

EMERGING SCIENCE PLATFORM SESSION
Tuesday, May 7, 2019, 11:45 a.m.-12:45 p.m.

001 Efficacy and safety of PXT3003 in patients with Charcot-Marie-Tooth type 1A (CMT1A): results of PLEO-CMT, an International Pivotal Phase 3 Trial *Florian P. Thomas, MD, MA, PhD, FAAN*

002 SerumLincLNMAT1Correlated with Phosphorylatedα-Synucleinas Serum Biomarkers of Parkinson's Disease: A Cross-Sectional Study. *Jing Zou, MD, PhD, MBBS*

003 Development of an AAV-based microRNA Gene Therapy for Treating Spinocerebellar Ataxia Type 3 *Melvin Evers, PhD*

004 STARS: Results from a safety and efficacy study of OV101 (gaboxadol) in adults and adolescents with Angelman syndrome *Lynne Bird, MD*

005 Efficacy, Safety, and Tolerability of Rimegepant 75 mg Orally Dissolving Tablet for the Acute Treatment of Migraine: Results from a Phase 3, Double-Blind, Randomized, Placebo-Controlled Trial, Study 303 *Richard B Lipton, MD, FAAN*

006 Cannabidiol (CBD; 10 and 20mg/kg/day) significantly reduces convulsive seizure frequency in children and adolescents with Dravet syndrome (DS): Results of a dose-ranging, multi-center, randomized, double-blind, placebo-controlled trial (GWPCARE2) *Ian Miller, MD*

007 Safety, PK, PD, and exploratory efficacy in single and multiple dose study of a SOD1 antisense oligonucleotide (BIIB067) administered to participants with ALS *Timothy M. Miller, MD, PhD*

008 Zilucoplan, a Subcutaneously Self-Administered Peptide Inhibitor of Complement Component 5 (C5), for the Treatment of Generalized Myasthenia Gravis: Results of a Phase 2 Randomized, Double-Blind, Placebo-Controlled Trial and Open-Label Long-Term Extension *James F. Howard, Jr., MD, FAAN*

009 Efficacy and safety of eculizumab in aquaporin-4 antibody positive (AQP4-IgG+) neuromyelitis optica spectrum disorder (NMOSD): a phase 3, randomized, double-blind, placebo-controlled, multicenter trial (PREVENT) *Sean J. Pittock, MD*

010 Kelch-like protein 11 autoantibodies are a novel biomarker of testicular cancer-associated paraneoplastic encephalitis *Divyanshu Dubey, MD*

011 MODULATION OF CSF CASPASE-3 IN MSC-NTF CELLS (NUROWN®) IN A PHASE 2 ALS STUDY: CORRELATIONS WITH CSF BIOMARKERS AND CLINICAL RESPONSE *Ralph Z. Kern, MD*

CLINICAL TRIALS PLENARY SESSION
Tuesday, May 7, 2019, 9:15 a.m. – 11:30 a.m.
AA Phase 3 study of isradipine as a disease modifying agent in patients with early Parkinson's disease (STEADY-PD III): Final study results *Tanya Simuni, MD, Parkinson Study Group*

001

11:45 a.m. – 11:48 a.m.

EMBARGOED FOR RELEASE UNTIL 12:01 AM EST ON FRIDAY, MAY 3, 2019

Efficacy and safety of PXT3003 in patients with Charcot-Marie-Tooth type 1A (CMT1A): results of PLEO-CMT, an International Pivotal Phase 3 Trial

Florian P. Thomas, MD, MA, PhD, FAAN, Youcef Boutalbi, Serge Fitoussi, Philippe Rinaudo, Viviane Bertrand, Rodolphe Hajj, Serguei Nabirotchkin, Daniel H. Cohen, MD, PhD

Objective: To assess the effect of PXT3003 on disability measured by the mean change from baseline of Overall Neurology Limitations Scale (ONLS) score at month 12 and 15. Effects on the 10-meter Walk Test (10-mWT) constituted one of the secondary efficacy endpoints. **Background:** CMT1A is a rare, inherited, chronic, peripheral neuropathy affecting 1 in 5000 patients. Patients suffer from distal-dominant muscle atrophy compromising gait and activities of daily living, stocking-glove sensory loss, and overall reduced quality of life. To date, no treatment is available to stabilize or reverse the disease. PXT3003 is a novel oral fixed-dose 3 drug combination: baclofen, naltrexone and D-sorbitol targeting multiple disease pathways. **Design/Methods:** PLEO-CMT is an international, multi-center, randomized, double-blind, placebo (Pb)-controlled pivotal phase III trial, assessing the efficacy and safety of 2 doses of PXT3003 given twice daily for up to 15 months to mild-to-moderate severity, genetically confirmed, CMT1A patients aged 16 to 65, with Dose 1 (D1) (3 mg baclofen, 0.35 mg naltrexone and 105 mg sorbitol). and Dose 2 (D2) at twice D1. **Results:** 323 patients were randomized 1:1:1 in the study (D1=109, D2=113, Pb=101). Characteristics of the three groups were comparable at baseline. PXT3003 D2 met the primary endpoint: a clinically meaningful reduction of 0.37-point ONLS (95% CI [0.1,0.64], p=0.008) was observed vs. Pb. In addition, in group D2 a trend for improvement was observed vs. baseline at -0.20-point ONLS (95% CI [-0.447, -0.039], p=0.098). A reduction of 0.47 sec (95%CI [0.09,0.85], p=0.016) was observed on the 10-mWT with D2 vs. Pb. The rate of treatment-emergent adverse events leading to treatment withdrawal was low and similar between groups (D2=5.3%, D1=5.5%, Pb=5.6%). **Conclusions:** PXT3003 is the first treatment for CMT1A demonstrated to be effective, safe and well tolerated.
Study Supported By: Pharnext
Disclosures: Dr. Thomas has received personal compensation for consulting, serving on a scientific advisory board, speaking, or other activities with Acceleron Pharma, Acorda Therapeutics, Genentech, Genzyme, Novartis, Pharnext and Teva Neuroscience. Dr. Thomas has received research support from Biogen and Teva Neuroscience, Dr. Boutalbi has received personal compensation for consulting, serving on a scientific advisory board, speaking, or other activities with Pharnext, Dr. Fitoussi has received personal compensation for consulting, serving on a scientific advisory board, speaking, or other activities with GenSight Biologics, Pharnext, Dr. Rinaudo has received personal compensation for consulting, serving on a scientific advisory board, speaking, or other activities with Pharnext, Dr. Bertrand has received personal compensation for consulting, serving on a scientific advisory board, speaking, or other activities with Pharnext, Dr. Hajj has received personal compensation for consulting, serving on a scientific advisory board, speaking, or other activities with Pharnext, Dr. Nabirotchkin has received personal compensation for consulting, serving on a scientific advisory board, speaking, or other activities with Pharnext, Dr. Cohen has received personal compensation for consulting, serving on a scientific advisory board, speaking, or other activities with Pharnext.

002

11:48 a.m. – 11:51 a.m.

EMBARGOED FOR RELEASE UNTIL 12:01 AM EST ON FRIDAY, MAY 3, 2019

SerumLincLNMAT1Correlated withPhosphorylatedα-SynucleinasSerum Biomarkers of Parkinson's Disease: A Cross-Sectional Study

Jing Zou, MD, PhD, MBBS, Zhenze Lu, Lei Wei, Lin Li, Anding Xu, PhD

Objective: In this study, we report that a long noncoding RNA, lincLNMAT1 in serum involved in the diagnosis of Parkinson's disease (PD) and correlated with serum phosphorylated α-synuclein (PS-129 α-Syn) in PD. **Background:** Early diagnosis of PD is an important issue to improve the prognosis. PS-129 α-Syn is one of posttranslational modifications to α-synuclein that may be critical in PD pathogenesis. Long noncoding RNA (lncRNA) has also been reported to have a function in the pathogenesis of PD**. Design/Methods:** In this study, we detected serum lincLNMAT1 expression in 189 PD patients and 161 healthy volunteers by using the quantitative real-time polymerase chain reaction (qRT-PCR) method. Serum PS-129 α-Syn concentrations were measured by ELISA assay. Receivers operating characteristic (ROC) curves were applied to map the diagnostic accuracy of PD patients compared to healthy subjects. Several scales were used to rate the severity of PD patients. **Results:** The expression level of serum lincLNMAT1 (0.196 ± 0.018) was significantly higher in PD patients compared with that of healthy controls (0.042 ± 0.005). Serum PS-129 α-Syn level was also found to be higher in PD patients (36.18 ± 2.62 ng/μL) than healthy controls (30.05 ± 2.11 ng/μL). Clinical data indicated that serum lincLNMAT1 was positively correlated with H&Y stage and the unified Parkinson's disease rating scale III (UPDRS III) score. Moreover, there was a significant positive correlation between serum lincLNMAT1 levels and serum PS-129 α-Syn according to Spearman's rank correlation analysis. The ROC curve for lincLNMAT1 (AUC 0.793) showed potential diagnostic value in discriminating PD from healthy subjects. **Conclusions:** Our study, for the first time, demonstrated that serum lincLNMAT1 might serve as a potent serum protein marker for the diagnosis of PD.
Study Supported By: The National Natural Science Foundation of China (no. 81671167), the Natural Science Foundation of Guangdong Province (no. 2014A030313384) and the Science and Technology Program of Guangzhou, China (nos. 201508020004, 2014Y2-00505 and 2017A020215049)
Disclosures: Dr. Zou has nothing to disclose, Dr. Xu has nothing to disclose.

003

11:51 a.m. – 11:54 a.m.

EMBARGOED FOR RELEASE UNTIL 12:01 AM EST ON FRIDAY, MAY 3, 2019

Development of an AAV-based microRNA Gene Therapy for Treating Spinocerebellar Ataxia Type 3

Melvin Evers, PhD, Raygene Martier, Janice Stricker-Shaver, Jeannette Hübener-Schmid, Sonay Keskin, Sander van Deventer, Huu Phuc Nguyen, Joseph J. Higgins, MD, FAAN, Pavlina Konstantinova

Objective: To lower the expression of toxic ataxin-3 protein in a spinocerebellar ataxia type 3 (SCA3) knock-in mouse model by intrathecal gene therapy. **Background:** SCA3, or Machado-Joseph disease (MJD), is a fatal neurodegenerative disorder characterized by brain stem and cerebellar atrophy. Clinical manifestations predominantly include progressive gait ataxia with the involvement of cranial nerves. An expansion of a CAG trinucleotide repeats in the ataxin-3 gene (ATXN3) causes the accumulation of aberrant, toxic ATXN3 protein in brain regions located in the posterior fossa. **Design/Methods:** A non-allele-specific ATXN3 silencing approach was investigated using artificial microRNAs engineered to target various regions of the ATXN3 gene (miATXN3). The miATXN3 candidates were screened in vitro for their silencing efficacies by using a luciferase reporter co-expressing ATXN3. Three miATXN3 candidates were selected for further testing and packaged into AAV5 (AAV5-miATXN3). The AAV5-miATXN3 candidates were tested for target engagement and potential off-target activity in neurons differentiated from induced pluripotent stem cells (iPSCs). In vivo reduction of mutant ataxin-3 was tested in a SCA3 knock-in mouse model by intraventricular, intracisternal and cerebellar intraparenchymal AAV5-miATXN3 infusions. **Results:** Small RNA sequencing showed efficient guide strand processing without any passenger strands. The AAV5-miATXN3 candidates strongly reduced ATXN3 mRNA in the iPSCs-derived neurons. Intracisternal AAV5-miATXN3 administration resulted in the most effective reduction (up to 65%) of mutant ataxin-3 protein in the cerebellum and brain stem. **Conclusions:** Intracisternal administration of AAV5-miATXN3 significantly lowers mutant ATXN3 protein in the primary sites of SCA3 neuropathology. These results provide evidence to further investigate the distribution, efficacy, tolerability, and safety of AAV5-miATXN3 in larger animals.
Study Supported By: uniQure
Disclosures: Dr. Evers has received personal compensation for consulting, serving on a scientific advisory board, speaking, or other activities with uniQure. Dr. Evers has received compensation for serving on the Board of Directors of uniQure. Dr. Evers holds stock and/or stock options in uniQure, Inc. which sponsored research in which Dr. Evers was involved as an investigator. Dr. Evers has received research support from uniQure, Inc., Dr. van Deventer has received personal compensation for consulting, serving on a scientific advisory board, speaking, or other activities with uniQure, Inc., Dr. van Deventer has received compensation for serving on the Board of Directors of uniQure, Inc., Dr. van Deventer has received royalty, license fees, or contractual rights payments from uniQure, Inc., Dr. van Deventer holds stock and/or stock options in uniQure, Inc. which sponsored research in which Dr. van Deventer was involved as an investigator, Dr. van Deventer has received research support from uniQure, Inc., Dr. Higgins has received personal compensation for consulting, serving on a scientific advisory board, speaking, or other activities with uniQure. Dr. Higgins holds stock and/or stock options in uniQure, which sponsored research in which Dr. Higgins was involved as an investigator. Dr. Higgins has received research support from uniQure, Inc., Dr. Konstantinova has received personal compensation for consulting, serving on a scientific advisory board, speaking, or other activities with uniQure, Inc., Dr. Konstantinova has received compensation for serving on the Board of Directors of uniQure, Inc., Dr. Konstantinova has received royalty, license fees, or contractual rights payments from uniQure, Inc., Dr. Konstantinova holds stock and/or stock options in uniQure, Inc. which sponsored research in which Dr. Konstantinova was involved as an investigator, Dr. Konstantinova has received research support from uniQure, Inc..

004

11:54 a.m. – 11:57 a.m.

EMBARGOED FOR RELEASE UNTIL 12:01 AM EST ON FRIDAY, MAY 3, 2019

STARS: Results from a safety and efficacy study of OV101 (gaboxadol) in adults and adolescents with Angelman syndrome

Lynne Bird, MD, Cesar Ochoa-Lubinoff, Wen-Hann Tan, Gali Heimer, Raun Melmed, Jeannie Visootsak, Matthew During, Rebecca Burdine, Alexander Kolevzon, Ronald L. Thibert, DO

Objective: To evaluate the safety, tolerability, and efficacy of OV101 (gaboxadol) in adult and adolescent patients with Angelman syndrome (AS). **Background:** AS is a rare, genetic, neurodevelopmental disorder caused by a deficient UBE3A allele, characterized by intellectual disability, seizures, severe impairments in speech, behavior, motor skills, and sleep. OV101 is an extrasynaptic delta-selective GABAA receptor agonist with the potential to normalize tonic inhibition, which has previously been shown to be decreased in AS. **Design/Methods:** STARS was a phase 2, randomized, double-blinded, placebo-controlled trial of OV101 QD (15 mg) and BID (10 mg, 15 mg) vs placebo. The primary objective was safety and tolerability over 12 weeks. Exploratory objectives included efficacy assessments on motor function, sleep, and behavior using the Clinical Global Impressions - Improvement scale (CGI-I) and domain specific instruments. **Results:** Seventy-eight patients completed the study. Most AEs were mild with similar frequencies observed between the groups. Global improvement, as captured by CGI-I was observed at Week 12 with OV101 QD vs placebo (P=0.0006). Additional post-hoc analyses showed improvements in sleep onset latency and overall sleep and motor function. The Parent Global Impressions suggests that patients who show a clinically meaningful improvement on CGI-I (<2), also demonstrate improvements in communication, challenging behavior, and anxiety. **Conclusions:** STARS is the first trial to demonstrate clinical benefit of OV101 in patients with AS, with improvements observed in sleep, motor, and behavior. These data suggest that CGI-I may be particularly well suited for assessing clinical improvements in a highly heterogeneous disorder like AS and may serve as a primary endpoint in future clinical trials. CGI-I offers the opportunity to assess each individual as their own control, and measure improvement across multiple symptom domains. The results support further development of OV101 and the continued use of CGI-I as a clinical endpoint for individuals with AS.
Study Supported By: Study supported by Ovid Therapeutics.
Disclosures: Dr. Bird has received personal compensation for consulting, serving on a scientific advisory board, speaking, or other activities with Neuralstem – Consultant FDNA, Millendo Therapeutics, Inc., Connected Research Consulting, Cello Health Bioconsulting, Dr. Bird has received research support from Ovid Therapeutics, Inc., Millendo Therapeutics Inc., Soleno Therapeutics, Inc., Insys Therapeutics, Inc., Levo Therapeutics, Inc., Eli Lilly GLWL Research, Inc., Dr. Ochoa-Lubinoff participated in an advisory board and consulted for Ovid Therapeutics. Dr. Ochoa-Lubinoff has received research support from Ovid Therapeutics, Dr. Tan received honorarium from Ovid Therapeutics and Roche for participation on advisory boards and received honorarium from Gerson Lehrman Group and Now What Research for consulting services. Dr. Tan received research support from Ovid Therapeutics, Dr. Visootsak is a full-time employee at Ovid Therapeutics. Dr. Visootsak is a full-time employee at Ovid Therapeutics, Dr. During is a >5% shareholder on the basis of being the founder of Ovid Therapeutics (OVID, Nasdaq), Dr. Burdine is a paid coach for the faculty training program at the National Center for Faculty Development and Diversity. Dr. Burdine has consulted for Ovid Therapeutics. Dr. Burdine's husband was a shareholder in GeneWiz, Inc., Dr. Kolevzon has received personal compensation for consulting, serving on a scientific advisory board, speaking, or other activities with Ovid Therapeutics, Coronis Neurosciences, 5AM Ventures, SEMA4, and Labcorp. Dr. Kolevzon has received research support from Amo Pharma, Dr. Thibert consulted for Ovid Therapeutics.

005

11:57 a.m. – 12:00 p.m.

EMBARGOED FOR RELEASE UNTIL 12:01 AM EST ON FRIDAY, MAY 3, 2019

Efficacy, Safety, and Tolerability of Rimegepant 75 mg Orally Dissolving Tablet for the Acute Treatment of Migraine: Results from a Phase 3, Double-Blind, Randomized, Placebo-Controlled Trial, Study 303

Richard B. Lipton, MD, FAAN, Vladimir Coric, Elyse Stock, David Stock, Alexandra Thiry, Charles Conway, Gene Dubowchik, Christopher Jensen, PharmD, Ralph Gosden, Marianne Frost, Kimberly Gentile, Beth Morris, Micaela Forshaw, Robert Croop, MD

Objective: Compare the efficacy, safety, and tolerability of rimegepant 75 mg orally dissolving tablet (ODT) with placebo in the acute treatment of migraine. **Background:** Rimegepant is a small molecule calcitonin gene-related peptide (CGRP) receptor antagonist with demonstrated efficacy in the acute treatment of migraine. An ODT formulation with a T_{max} 30 minutes earlier than the previously studied tablet may have a more rapid onset of action. **Design/Methods:** This double-blind, randomized, placebo-controlled, multicenter Phase 3 trial (Study 303, NCT03461757) included adults ³18 years of age with ³1-year history of migraine. Subjects randomized to rimegepant 75 mg ODT or placebo treated 1 migraine attack of moderate or severe pain intensity. The coprimary endpoints were 2-hour pain freedom and freedom from the most bothersome symptom (MBS). Safety assessments included adverse events (AEs), ECGs, vital signs, and routine laboratory tests. **Results:** Altogether, 1375 subjects were randomized and treated; 1351 were evaluated for efficacy (rimegepant n=669, placebo n=682). Mean age was 40 years; subjects were 85% female. Rimegepant ODT was superior to placebo for 2-hour pain freedom (21.2% vs 10.9%, *P*<.0001) and freedom from the MBS (35.1% vs 26.8%, *P*=.0009). Additionally, rimegepant ODT significantly outperformed placebo for 60-minute pain relief (*P*=.0314) and functional disability freedom (*P*=.0025); 90-minute pain freedom (*P*<.0001) and MBS freedom (*P*=.0128); and 48-hour sustained pain freedom (*P*<.0001), sustained pain relief (*P*<.0001), sustained MBS freedom (*P*=.0018), and sustained functional disability freedom (*P*<.0001). The most common AEs were nausea and urinary tract infection occurring ≤1.6%. No serious treatment emergent AEs were reported. **Conclusions:** A single dose of rimegepant ODT achieved its coprimary endpoints and demonstrated rapid and sustained clinical benefits within 60 minutes and through 48 hours postdose. These results suggest that rimegepant ODT has a fast onset and placebo-like tolerability in the acute treatment of migraine.
Study Supported By: Biohaven Pharmaceuticals
Disclosures: Dr. Lipton has received personal compensation for consulting, serving on a scientific advisory board, speaking, or other activities with Serves as consultant, advisory board member, or has received honoraria from: American Academy of Neurology, Alder, Allergan, American Headache Society, Amgen, Autonomic Technologies, Avanir, Biohaven, Biovision, Boston Scientific, Dr. Reddy's, Electrocore, Eli Lilly, eNeura Therapeutics, GlaxoSmithKline, Merck, Pernix, Pfizer, Supernus, Teva, Trigemina, Vector, Vedanta.. Dr. Lipton has received compensation for serving on the Board of Directors of eNeura, Biohaven. Dr. Lipton holds stock and/or stock options in Biohaven which sponsored research in which Dr. Lipton was involved as an investigato. Dr. Lipton holds stock and/or stock options in Biohaven. Dr. Lipton has received research support from Receives support from the Migraine Research Foundation, the National Headache Foundation and Amgen., Dr. Stock, MD, is employed by and holds stock/stock options in Biohaven Pharmaceuticals, Dr. Jensen, PharmD, is employed by and holds stock/stock options in Biohaven Pharmaceuticals, Dr. Gentile, BS, is employed by and holds stock/stock options in Biohaven Pharmaceuticals. Dr. Gentile holds stock and/or stock options in Biohaven Pharmaceuticals, Dr. Croop, MD, is employed by and holds stock/stock options in Biohaven Pharmaceuticals.

006

12:00 p.m. – 12:03 p.m.

EMBARGOED FOR RELEASE UNTIL 12:01 AM EST ON FRIDAY, MAY 3, 2019

Cannabidiol (CBD; 10 and 20mg/kg/day) significantly reduces convulsive seizure frequency in children and adolescents with Dravet syndrome (DS): Results of a dose-ranging, multi-center, randomized, double-blind, placebo-controlled trial (GWPCARE2)

Ian Miller, MD, M. Scott Perry, MD, Russell P. Saneto, DO, PhD, Ingrid Scheffer, Boudewijn Gunning, Rocio Sanchez-Carpintero, Antonio Gil-Nagel, MD, Daniel Checketts, Lauren Whyte, Eduardo Dunayevich, Volker A. Knappertz, MD

Objective: Assess the efficacy and safety of 2 doses of cannabidiol (CBD) as an add-on anticonvulsant therapy in patients with Dravet syndrome (DS) and drug-resistant seizures. **Background:** DS is an infantile onset developmental and epileptic encephalopathy associated with drug-resistant seizures. **Design/Methods:** 199 patients were randomized to receive highly purified CBD (approved as Epidiolex® in the U.S.) at 20 mg/kg/day (CBD20; n=67), 10 mg/kg/day (CBD10; n=67), or placebo (pbo; n=65). The primary endpoint was the change in convulsive seizure frequency over the 14-week treatment period compared to a 4-week baseline. **Results:** Mean age was 9 years. Patients were currently taking a median of 3 antiepileptic drugs (AEDs), having discontinued a median of 4 previously. Percentage reduction in convulsive seizures was higher for both CBD20 (46%) and CBD10 (49%) vs. pbo (27%; p=0.0299 and p=0.0095), as were ≥50% responder rates (49% and 44% vs. 26%; p=0.0069 and p=0.0332) and % reduction in total seizures (47% and 56% vs. 30%; p=0.0255 and p=0.0003).
The incidence of adverse events (AEs) was similar across all groups (90% CBD20, 88% CBD10, 89% pbo). The 5 most common AEs were decreased appetite, diarrhea, somnolence, pyrexia, and fatigue. Serious AEs were reported in 25% CBD20, 20% CBD10, and 15% pbo patients. Discontinuations due to AEs only occurred for CBD20 patients (7%). Elevated transaminases exceeding 3× upper limit of normal (ULN) occurred in 19% CBD20 and 5% CBD10 patients; none had elevations in bilirubin; all were taking concomitant valproate; all elevations resolved. There were no deaths.
Conclusions: CBD20 and CBD10significantlyreducedseizure frequency versus pbo. Elevated transaminases and certain AEs and discontinuations due to AE occurred more frequently for CBD20 than CBD10 or placebo. Dose increases above10 mg/kg/day should be tailored to individual efficacy and safety.
Study Supported By: Supported by GW Research Ltd, operating in the U.S. through its affiliate, Greenwich Biosciences, Inc.; NCT02224703
Disclosures: Dr. Miller has received personal compensation for consulting, serving on a scientific advisory board, speaking, or other activities with Insys pharmaceuticals, GWPharma, TS Alliance, DS Foundation, Visualase, Neuroblate, Zogenix, and Ultragenix. Dr. Miller has received personal compensation for consulting, serving on a scientific advisory board, speaking, or other activities with Insys pharmaceuticals, GWPharma, TS Alliance, DS Foundation, Visualase, Neuroblate, Zogenix, and Ultragenix. Dr. Miller has received research support from Insys pharmaceuticals, GWPharma, TS Alliance, DS Foundation, Visualase, Neuroblate, Zogenix, and Ultragenix, Dr. Perry has received personal compensation for consulting, serving on a scientific advisory board, speaking, or other activities with Upsher Smith. Zogenix – Advisory Board Conducted Phase III clinical trials for Greenwich Biosciences Inc, Zogenix, Dr. Saneto Greenwich Biosciences Inc. - speaker's bureau was a PI on the GW studies for Dravet and TSC; PI on a clinical study sponsored by REATA for Friedreich Ataxia; PI on a study sponsored by Stealth Pharmaceutical for primary mitochondrial myopathy; PI on as study sponsored by Zogenix in patients with Dravet syndrome, Dr. Sanchez-Carpintero has received personal compensation for consulting, serving on a scientific advisory board, speaking, or other activities with advisory board for Novartis, for GWPharma and for Zogenix Dr. Sanchez-Carpintero has received research support from GWpharma and Zogenix for clinical trials, Dr. Gil-Nagel has received personal compensation for consulting, serving on a scientific advisory board, speaking, or other activities with Eisai, European Dravet Foundation, UCB, GW Pharma, Zogenix Research funding, Eisai, UCB, Dr. Checketts has received personal compensation for consulting, serving on a scientific advisory board, speaking, or other activities with GW Research Ltd. Dr. Checketts holds stock and/or stock options in GW Pharmaceuticals, Dr. Whyte has received personal compensation for consulting, serving on a scientific advisory board, speaking, or other activities with GW Pharmaceuticals plc. Dr. Whyte holds stock and/or stock options in GW Pharmaceuticals plc, Dr. Knappertz has received personal compensation for consulting, serving on a scientific advisory

board, speaking, or other activities with Employed by Greenwich Biosciences Inc.. Dr. Knappertz holds stock and/or stock options in Knopp Biosciences; TEVA pharmaceuticals; GW Pharmaceuticals.

007

12:03 p.m. – 12:06 p.m.

EMBARGOED FOR RELEASE UNTIL 12:01 AM EST ON FRIDAY, MAY 3, 2019

Safety, PK, PD, and exploratory efficacy in single and multiple dose study of a SOD1 antisense oligonucleotide (BIIB067) administered to participants with ALS

*Timothy M. Miller, MD, PhD, Merit E. Cudkowicz, MD, MSC, Pamela Jean Shaw, MD, FRCP, FAAN, Danielle Graham, Stephanie Fradette, Hani Houshyar, Frank Bennett, PhD, Roger M. Lane, MD, MPH, Ivan Nestorov, Laura Fanning, Ih Chang, Toby Ferguson *On behalf of the 233AS101 Study Investigators*

Objective: To evaluate the safety, tolerability, pharmacokinetics (PK), and pharmacodynamics (PD) of an antisense oligonucleotide (BIIB067) designed to reduce superoxide dismutase (SOD1) mRNA in people with amyotrophic lateral sclerosis (ALS) with SOD1 gene mutation (SOD1-ALS). **Background:** ALS is a fatal, neurodegenerative disease characterized by loss or dysfunction of upper and lower motor neurons. Approximately 2% of ALS cases are linked to SOD1 mutations. Over 200 SOD1 mutations have been identified with substantial variation in rate of disease progression. Toxicity of mutant SOD1 is secondary to gain of function, not loss of SOD activity, suggesting SOD1 reduction may be therapeutic. BIIB067 is under development for treatment of SOD1-ALS. **Design/Methods:** This randomized, placebo-controlled, single- and multiple-ascending dose (SAD/MAD) study enrolled participants with ALS. In the MAD portion of the study, 50 participants with confirmed SOD1 mutation were randomized (3:1 BIIB067:placebo) to receive BIIB067 (20, 40, 60, or 100 mg) or placebo for 12 weeks. Safety (primary), PK/PD (secondary), and efficacy (exploratory) were assessed. **Results:** The majority of adverse events (AEs) were mild or moderate in severity. Dose-dependent increases in BIIB067 concentrations in plasma and CSF were observed. A statistically significant reduction of CSF SOD1 was observed in the 100-mg cohort (n=10) versus placebo (n=12) (p=0.002) and suggested substantial reduction of CNS tissue SOD1. Lowering of CSF phosphorylated neurofilament heavy and slowing of functional decline as measured by ALS Functional Rating Scale Revised scores, slow vital capacity, and muscle strength were observed in the 100-mg cohort versus placebo. In participants with SOD1 mutations known to be rapidly progressive, a greater difference between the 100 mg and placebo groups was observed across these measures compared to those with other mutations. **Conclusions:** This first report of BIIB067 in SOD1-ALS demonstrates reduction of SOD1 in CSF and strongly supports further investigation of BIIB067 efficacy in people with SOD1-ALS.

Study Supported By: Biogen

Disclosures: Dr. Miller is on Biogen, medical advisory board. Cytokinetics, consultant Licensing agreement with C2N, licensing agreement with Ionis Pharmaceuticals Biogen, clinical research support. Ionis, provided reagents. Site PI for clinical trials for Orion, Amylyx, Dr.Cudkowiz is on Biohaven, Takeda, Avexis, Lilly, Biogen (advisory board), Aclipse, Dr. Shaw is on Consultancy for serving on Scientific Advisory Board for Biogen and for speaking, symposium organisation for Cytokinetics. Research support from Pfizer for investigation of molecular mechanisms of neuronal injury in C9orf72 ALS, Dr. Graham is an employee of and hold stock/stock options in Biogen. Dr. Fradette is an Employee of and hold stock/stock options in Biogen. Biogen, compensation includes stock. Biogen, stock greater than 10K, Dr. Houshyar has received personal compensation for consulting, serving on a scientific advisory board, speaking, or other activities with Biogen, Dr. Houshyar is an employee of and/or holds stock with Biogen. Dr. Bennett is an Employee of and hold stock/stock options in Ionis, Dr. Lane is an Employees of and hold stock/stock options in Ionis. Ionis, compensation includes salary and stock options. RL: Ionis, compensation includes salary and stock options that exceed $10,000 in value. Ionis, compensation includes salary and stock options that exceed $10,000 in value, Dr. Nestorov is an Employees of and hold stock/stock options in Biogen, Dr. Fanning is an Employees of and hold stock/stock options in Biogen, Dr. Chang is an Employee of and hold stock/stock options in Biogen. Biogen, stock greater than 10K. Dr. Ferguson has received personal compensation for consulting, serving on a scientific advisory board, speaking, or other activities with Biogen. Dr. Ferguson holds stock and/or stock options in Biogen which sponsored research.

008
12:06 p.m. – 12:09 p.m.

EMBARGOED FOR RELEASE UNTIL 12:01 AM EST ON FRIDAY, MAY 3, 2018

Zilucoplan, a Subcutaneously Self-Administered Peptide Inhibitor of Complement Component 5 (C5), for the Treatment of Generalized Myasthenia Gravis: Results of a Phase 2 Randomized, Double-Blind, Placebo-Controlled Trial and Open-Label Long-Term Extension

James F. Howard, Jr., MD, FAAN, Richard J. Nowak, MD, Gil I. Wolfe, MD, FAAN, Michael G. Benatar, MBChB, DPhil, FAAN, Petra W. Duda, MD, PhD, James MacDougall, Ramin Farzaneh-Far, Henry J. Kaminski, MD, FAAN

Objective: To evaluate the safety, tolerability, and preliminary efficacy of zilucoplan, a subcutaneously self-administered peptide inhibitor of C5, in patients with generalized myasthenia gravis (gMG). **Background:** In gMG, autoantibodies against the acetylcholine receptor (AChR-Ab) trigger complement-mediated damage to the neuromuscular junction, leading to weakness. Zilucoplan binds to C5 and inhibits its activation, thereby preventing formation and assembly of the membrane attack complex. **Design/Methods:** We conducted a randomized, double-blind, placebo-controlled trial in AChR-Ab+ patients with Quantitative Myasthenia Gravis (QMG) scores ≥12, regardless of their prior treatment history, to evaluate the safety, tolerability and efficacy of zilucoplan. The primary and key secondary endpoints were change from baseline to Week 12 in QMG and MG Activities of Daily Living (MG-ADL) scores. Significance testing was pre-specified at a 1-sided alpha of 0.1. Following completion of the 12-week study, subjects were eligible to enter a long-term open-label extension (OLE). **Results:** Forty-four patients were randomized 1:1:1 to placebo, zilucoplan 0.1 mg/kg, or zilucoplan 0.3 mg/kg subcutaneously (SC) daily over 12 weeks. Clinically meaningful and statistically significant improvements in the primary and key secondary efficacy endpoints were observed. Zilucoplan dosed at 0.3 mg/kg SC daily achieved a mean reduction from baseline of 6.0 points in the QMG score (placebo-corrected change: -2.8; p=0.05) and a mean reduction from baseline of 3.4 points in the MG-ADL score (placebo-corrected change: -2.3; p=0.04). Rescue therapy (intravenous immunoglobulin or plasma exchange) was required in 3/15 subjects in the placebo arm, 1/15 in the 0.1 mg/kg zilucoplan arm, and 0/14 in the 0.3 mg/kg zilucoplan arm. Zilucoplan was observed to have a favorable safety and tolerability profile, consistent with prior clinical trials. Long-term data from the OLE will also be presented. **Conclusions:** These positive data support the potential therapeutic role of zilucoplan in gMG and its further evaluation in a registrational Phase 3 trial.

Study Supported By: Ra Pharmaceuticals

Disclosures: Dr. Howard has received personal compensation for consulting, serving on a scientific advisory board, speaking, or other activities with Alexion Pharmaceuticals. Dr. Howard holds stock and/or stock options in AT&T, General Electric, Pfizer, Johnson & Johnson. Dr. Howard has received research support from Alexion Pharmaceuticals, argenx BVBA, Ra Pharmaceuticals, Muscular Dystrophy Association, Dr. Nowak has received personal compensation for consulting, serving on a scientific advisory board, speaking, or other activities with Alexion, Ra Pharma, Momenta, Grifols, Roivant. Dr. Nowak has received research support from Alexion, Ra Pharma, Genentech, Grifols, Dr. Wolfe has received personal compensation for consulting, serving on a scientific advisory board, speaking, or other activities with Alexion Pharmaceuticals. Dr. Wolfe has received research support from Alexion Pharmaceuticals, Ra Pharmaceuticals, Dr. Benatar has received personal compensation for consulting, serving on a scientific advisory board, speaking, or other activities with Agency for Toxic Substances and Disease Registry, Anylam Pharmaceuticals, Avexis, Biogen Inc., Denali, Journal Watch Neurology, Mitsubishi Tanabe Pharma, Morris James LLC, Muscular Dystrophy Association, National Institute of Health, NMD Pharma, Ra Pharmaceuticals, US Department of Defense, UCB, UCB Biosciences Inc., Dr. Duda is an employee of Ra Pharmaceuticals. Dr. Duda holds stock and/or stock options in Ra Pharmaceuticals, Dr. MacDougall has received personal compensation for consulting, serving on a scientific advisory board, speaking, or other activities with Catabasis Pharmaceuticals and Ra Pharmaceuticals, Dr. Kaminski has received personal compensation for consulting, serving on a scientific advisory board, speaking, or other activities with Ra Pharmaceuticals, GT Biopharma, Alnylan, UCB.

009
12:09 p.m. – 12:12 p.m.

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Efficacy and safety of eculizumab in aquaporin-4 antibody positive (AQP4-IgG+) neuromyelitis optica spectrum disorder (NMOSD): a phase 3, randomized, double-blind, placebo-controlled, multicenter trial (PREVENT)

Sean J. Pittock, MD, Achim Berthele, MD, Kazuo Fujihara, MD, Ho Jin Kim, MD, Michael Levy, MD, FAAN, Jacqueline Palace, Ichiro Nakashima, MD, PhD, Murat Terzi, PhD, Natalia Totolyan, MD, Shanthi Viswanathan, Kai-Chen Wang, Roisin Armstrong, PhD, Kenji Fujita, Amy Pace, Dean M. Wingerchuk, MD, FAAN Klatt

Objective: Evaluate the efficacy and safety of eculizumab in adults with AQP4-IgG+ NMOSD (NCT01892345).
Background: Complement activation is a major component of CNS inflammation and astrocytic injury in patients with NMOSD. Eculizumab effectively inhibits C5 terminal complement activation. **Design/Methods:** PREVENT was a global phase 3, randomized, double-blind, study designed to end at 24on-trial relapses (adjudicated by blinded, independent, expert panel). Patients (aged ≥18 years) were randomized 2:1 to eculizumab (1200mg every 2weeks maintenance) or placebo. Stable-dose supportive immunosuppressive therapy (IST) was permitted. Patients receiving rituximab in the prior 3 months were excluded. **Results:** Overall, 213 patients were screened, 143 randomized (90.9% women, median age 45.0 years) and 124 completed the study (eculizumab 80/96 [83.3%], placebo 44/47 [93.6%]). Between-group baseline annualized relapse rates (ARRs) (eculizumab mean=1.94 [SD=0.896], placebo 2.07 [1.037]) and supportive IST use (eculizumab, 78.1% of participants; placebo, 72.3%) were similar. The study was stopped at 23 adjudicated on-trial relapses (eculizumab, n=3; placebo, n=20). Eculizumab had a significant effect on time to first adjudicated on-trial relapse (primary endpoint, $p<0.0001$), demonstrating a 94.2% reduction in relapse risk compared with placebo (HR, 0.058 [95% CI: 0.017-0.197]). At 48 weeks, 97.9% (95% CI: 91.8-99.5%) of eculizumab-treated participants were relapse-free compared with 63.2% (46.8-75.8%) for placebo. Adjudicated on-trial ARR (first secondary endpoint) was significantly lower with eculizumab (0.016 [95% CI: 0.005-0.050]) than placebo (0.350 [0.199-0.616]) (rate ratio, 0.045 [0.013-0.151], $p<0.0001$). For eculizumab and placebo groups, treatment exposure was 170.0 and 51.5 patient-years and treatment-emergent adverse event (TEAE) rates were 749.3 and 1160.9 per 100 patient-years, respectively. Most TEAEs were mild to moderate. One on-study death occurred in an eculizumab-treated patient (infectious pleural effusion). No meningococcal infections were reported. **Conclusions:** Eculizumab significantly reduced relapse risk in patients with AQP4-IgG+ NMOSD. The safety profile was similar to that in other indications.
Study Supported By: Alexion Pharmaceuticals, Inc.
Disclosures: Dr. Pittock has provided consultation to Alexion Pharmaceutical and MedImmune but has received no personal fees or compensation for these consulting activities. All compensation for consulting activities is paid directly to Mayo Clinic. Yes, Dr. Pittock receives research support from Alexion Pharmaceuticals, Medimmune and Grifols, Dr. Berthele has received personal compensation for consulting, serving on a scientific advisory board, speaking or other activities with Alexion, Bayer Healthcare, Biogen, Genzyme/Sanofi, Merck Serono, Novartis and Roche. Dr. Berthele has received research support from Chugai, Dr. Fujihara has received personal compensation from Biogen, Mitsubishi-Tanabe, Takeda, Novartis, Eisai, Nihon, Teijin, Ono, Asahi Medical, Apothecom, Dr. Kim has received personal compensation for consulting, serving on a scientific advisory board, speaking, or other activities with Celltrion, Eisai, HanAll BioPharma, MediImmune, Merck Serono, Novartis Pharmaceuticals, Sanofi Genzyme, and Teva-Handok. Dr. Kim has received personal compensation in an editorial capacity for co-editor for MS Journal-Experimental, Translational and Clinical and Journal of Clinical Neurology, Dr. Levy has received personal compensation for consulting, serving on a scientific advisory board, speaking, or other activities with Alexion, Acorda Therapeutics, Sanofi Genzyme, Quest Diagnostics. Dr. Levy has received research support from Sanofi Genzyme, Alexion, Alnylam Pharmaceuticals, Shire, Acorda Therapeutics, and Apopharma, Dr. Palace has received personal compensation for consulting, serving on a scientific advisory board, speaking, or other activities with Merck Serono, Biogen Idec, Novartis, Teva, Chugai Pharma and Bayer Schering, Alexion, Roche, Genzyme, MedImmune, EuroImmun, MedDay, Abide and ARGENX. Dr. Palace has received research support from MS society, Guthie Jackson Foundation, NIHR, Oxford Health Services Research Committee, EDEN, MRC, GMSI, and John Fell, Dr. Nakashima has received research support from LSI Medience Corporation, Dr. Terzi has nothing to disclose, Dr. Totolyan has received personal compensation for consulting, serving on a scientific advisory board, speaking, or other activities with Alexion, Merck, Roche, Sanofi, Janssen, Bayer, Teva, Novartis, GeNeuro, Dr. Armstrong has received personal compensation for consulting, serving on a scientific advisory

board, speaking or other activities with Alexion Pharmaceuticals Inc., Dr. Wingerchuk has received personal compensation from MedImmune, Celgene, and Novartis. Dr. Wingerchuk has received personal compensation in an editorial capacity as co-Editor-in-Chief for The Neurologist. Dr. Wingerchuk has received research support from Alexion and TerumoBCT.

010
12:12 p.m. – 12:15 p.m.

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Kelch-like protein 11 autoantibodies are a novel biomarker of testicular cancer-associated paraneoplastic encephalitis

Divyanshu Dubey, MD, Caleigh Mandel-Brehm, Thomas Kryzer, Brian O'Donovan, Baouyen Tran, Sara Vazquez, Hannah Sample, 14202, Kelsey Zorn, Lillian Kahn, Ian Bledsoe, Andrew McKeon, MD, Samuel J. Pleasure, MD, PhD, Manish Gandhi, Vanda A. Lennon, MD, PhD, Joseph DeRisi, PhD, Sean J. Pittock, MD, Michael R. Wilson, MD, FAAN

Objective: To evaluate for a novel autoantibody biomarker of paraneoplastic encephalitis and testicular cancer.
Background: Neural-specific autoantibody profiles provide actionable information regarding the etiology of a neurological syndrome, likelihood and type of associated neoplasm and immunotherapy response. To date, Ma2-IgG represent the only biomarker of paraneoplastic encephalitis and testicular germ cell tumors. **Design/Methods:** A human peptidome programmable phage display system identified a novel autoantibody among archived patient serum and CSF specimens that had yielded a distinctive sparse pattern referred to as the "Sparkles" on service tissue-based indirect immunofluorescence screening (substrate: adult mouse brain sections). Immunoprecipitation-mass spectrometry, commercial antibodies and transfected cell-based assays confirmed specificity. A population based seroprevalence study was performed. Human leukocyte antigen (HLA) association was ascertained by molecular typing of extracted DNA (7). **Results:** Kelch-like protein 11 (KLHL11)-IgG specificity, identified in 13 patients, was confirmed by patient CSF/serum immunoprecipitation of full-length KLHL11 protein and co-localization of patient-IgG and commercial KLHL11-IgG in KLH11-transfected cells. All patients had stereotypic neurological and oncologic profiles (8 testicular-seminomas, 3 extra-testicular seminomas, 2 testicular microlithiasis), and were Ma2-IgG negative. The median neurological symptom-onset age was 41 years (28-68 years). Most patients presented with ataxia (12/13), vertigo (8/13) and sensorineural hearing loss (7/13). CSF in all cases was inflammatory. The median interval between neurological symptom onset and tumor diagnosis was 6 months (range: -42 to +158 months). Despite treatment of seminoma, and immunotherapy, only one patient had significant clinical improvement. Age-adjusted male-specific prevalence of KLHL11 encephalitis in Olmsted County, Minnesota was 2.79/100,000 person-years. Five of 7 HLA-typed patients were major histocompatibility complex class 2 haplotype DR17~DQ2 positive. **Conclusions:** KLHL11-IgG represent the second biomarker for paraneoplastic encephalitis in men with testicular cancer.
Supported By: N/A
Dislcosures: Dr. Dubey has received research support from Grifols and Center of Multiple Sclerosis and Autoimmune Neurology, Dr. Kryzer has received royalty, license fees, or contractual rights payments from RSR, royalties from sale kits for AQP4 IgG detetction and from clinical service assays performed outside Mayo clinic, Dr. Sample has nothing to disclose, Dr. Zorn has nothing to disclose, Dr. McKeon has received research support from Medimmune, Euroimmun, Grifols and Alexion, Dr. Pleasure has nothing to disclose, Dr. Lennon has received royalty, license fees, or contractual rights payments from RSR, royalties from sale kits for AQP4 IgG detetction and from clinical service assays performed outside Mayo clinic, Dr. DeRisi Stock options received from uBiome, Inc. for Dr. DeRisi's role as a scientific consultant No. However, Dr. DeRisi currently serves on the Board of uBiome, Inc., but has not received compensation for doing so, to date. Yes. License of UCSF technology to Vela Operations Singapore Pte Ltd Yes. uBiome, Inc. Stock options were received as compensation for Dr. DeRisi's role as a scientific consultant, Dr Pittock has provided consultation to Alexion Pharmaceutical and MedImmune but has received no personal fees or compensation for these consulting activities. All compensation for consulting activities is paid directly to Mayo Clinic. Yes, Dr Pittock receives research support from Alexion Pharmaceuticals, Medimmune and Grifols, Dr. Wilson has received research support from Roche/Genentech.

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12:15 p.m. – 12:18 p.m.

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MODULATION OF CSF CASPASE-3 IN MSC-NTF CELLS (NUROWN®) IN A PHASE 2 ALS STUDY: CORRELATIONS WITH CSF BIOMARKERS AND CLINICAL RESPONSE

Ralph Z. Kern, MD, Revital Aricha, Haggai Kaspi, Merit E. Cudkowicz, MD, MSC, James D. Berry, MD MPH, Anthony J. Windebank, MD, FAAN, Nathan P. Staff, MD,PhD, FAAN, Margaret Ayo Owegi, Yossef Levy, Chaim Lebovits, Robert H. Brown, Jr., MD, D.Phil, Yael Gothelf

Objective: To measure CSF Caspase 3 levels pre- and post-single IT MSC-NTF cell transplantation and to correlate with clinical response and other CSF biomarkers. **Background:** MSC-NTF cells (NurOwn®) are autologous bone-marrow derived mesenchymal stem cells (MSC) that secrete high levels of neurotrophic factors (NTFs) and immunomodulatory cytokines having a signature miRNAs profile. MSC-NTF cells were administered by the intrathecal (IT) route of administration to participants in a US Phase 2 ALS multicenter double-blind placebo-controlled trial to evaluate safety and efficacy (NCT02017912). **Design/Methods:** CSF was collected prior to, and two weeks post-IT MSC-NTF cell transplantation. CSF Caspase-3, NTFs, cytokines and miRNAs were analyzed. Caspase-3 reduction was evaluated in responders (≥100% improvement in ALSFRS-R slope 12-weeks post transplantation) and non-responders. miR were analyzed in pooled CSF samples from responders, non-responders and placebo. **Results:** MCP-1 and Caspase-3 were significantly reduced post-transplantation in MSC-NTF treated participants and not in the placebo group. Expression of miR-132 was increased post -transplantation in MSC-NTF treated but not placebo participants. Baseline miR-132 was lower in non-responders compared to responders. Caspase-3 reduction was greater in responders compared to non-responders (69% vs. 38%, p=0.03). **Conclusions:** Decreased CSF Caspase-3 may reflect reduced neuronal apoptosis and serve as a biomarker for neuroprotection. While MSC-NTF cells may have anti-apoptotic effects through direct paracrine NTF mechanisms such as VEGF, it is possible that indirect effects may be mediated via immunomodulation and miR-132 secretion. Caspases are known to activate microglia via NF-kB signaling1 and miR-132 may regulate apoptotic genes2. miR-132 appears to be lower in the CSF of sporadic ALS patients3 and TDP-43 is required for the biogenesis of miR-1324. These findings support the combined immunomodulatory and neuroprotective mechanism of action of MSC-NTF cells through NTF, immunomodulatory and miRNA pathways.

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Clinical Trials Plenary Session

Tuesday, May 7, 2019, 9:15 a.m. – 11:30 a.m.

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A Phase 3 study of isradipine as a disease modifying agent in patients with early Parkinson's disease (STEADY-PD III): Final study results

Tanya Simuni, MD, Parkinson Study Group

Objective: To assess the efficacy of isradipine, a dihydropyridine calcium channel antagonist to slow the progression of Parkinson's disease (PD). **Background:** There remains no proven therapy to slow progression of Parkinson's disease (PD). **Design/Methods:** STEADY-PD III is an NINDS funded Phase 3, parallel group, 36 months study evaluating the efficacy of isradipine 10mg daily versus placebo (1:1 randomization, ITT analysis) to slow progression of disability in de novo PD participants. The study was conducted at 54 Parkinson Study Group sites in US and Canada. The primary outcome measure was the change from baseline in the Unified Parkinson Disease Rating Scale (UPDRS) Part I-III score measured in the ON state at month 36. Secondary outcomes include change in UPDRS-III in the OFF state, time to initiation and utilization of dopaminergic therapy, time to onset of motor complications, change in non-motor disability and quality of life measures. **Results**: The study enrolled 336 participants between November 2014 -November 2015, the last participant completed the study November 20, 2018. The study retention rate was 95%. Baseline demographic and disease characteristics including age 62 (SD=9), 68% male, 0.9 (SD=0.7) years from PD diagnosis, UPDRS I-III score =23.1 (SD=8.6) were well balanced between groups. Adjusted (by ANCOVA) mean UPDRS I-III medications ON changes over 36 months were 2.99 points (isradipine) and 3.26 points (placebo) with treatment effect of 0.27 points (95% CL's -2.5, 3.0, P =0.85). Key secondary outcomes showed no effect of isradipine treatment, Statistical adjustment for usage of symptomatic therapy did not affect the comparison. The most notable side effect of isradipine was edema. **Conclusions:** Isradipine 10 mg daily did not slow progression of disability in early PD. Secondary analysis is underway to explore biological and clinical correlates of disease progression in the study cohort.

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