Results of Transpher A, a Multicenter, Single-Dose, Phase 1/2 Clinical Trial of ABO-102 Gene Therapy for Sanfilippo Syndrome Type A (Mucopolysaccharidosis IIIA)

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Objective: To assess the efficacy and safety of ABO-102 in children with Mucopolysaccharidosis IIIA (MPS-IIIA).

Background: MPS-IIIA is a lysosomal storage disorder manifesting early in childhood with severe neurodegeneration.

Design/Methods: Transpher A is a Phase 1/2 clinical trial assessing the safety and efficacy of a single intravenous administration of ABO-102, a self-complementary AAV9-based vector encoding human SGSH, for treating MPS-IIIA. After 24 months, patients are transferred to a Long-Term Follow-Up study where they are monitored for 3 subsequent years. Primary endpoints are safety and neurocognitive development (compared to natural history studies), and secondary endpoints include additional cognitive and behavior evaluations as well as biomarker determination of brain and liver volume.

Results: Nineteen patients have been enrolled across three dose cohorts: Cohort 1, 5x1012 vg/kg, n=3; Cohort 2, 1x1013 vg/kg, n=3; Cohort 3, 3x1013 vg/kg, n=13. Cohorts 1 and 2, and 8 of 13 patients in Cohort 3 have completed 24-month follow-up. ABO-102 was well tolerated, with no serious drug-related adverse events (Follow-up Cohort 1: 53.5-56.7 months: Cohort 2: 45.5-48.1 months; Cohort 3: 1-42 months). Cohort 3 (the highest dose) was associated with rapid, dose-dependent, and statistically significant reductions of CSF heparan sulfate (HS) at all time points (including Month 24), as well as statistically significant reductions for systemic biomarkers (plasma and urine HS and total urine glycosaminoglycans) and liver volumes for the duration of follow-up. Neurocognitive evaluation showed

continuous developmental progress 30-36 months post-administration (43, 48 and 64 months of chronological age), a time at which they should be experiencing cognitive decline.

Conclusions: ABO-102 in MPS-IIIA patients showed a favorable long-term safety profile and led to statistically significant reductions in CNS and systemic biomarkers, with clear indications of meaningful neurocognitive benefit in the youngest patients treated with 3x1013 vg/kg, before advanced neurodegeneration.

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Preliminary Results of Ongoing, Prospective Study of Antibody and T-Cell Responses to SARS-CoV-2 in Patients With MS on Ocrelizumab or Other Disease-Modifying Therapies

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Objective: 1. To assess SARS-CoV-2 seropositivity in 1,000 patients with multiple sclerosis (MS) and its association with demographic and disease-related characteristics, and disease-modifying therapy (DMT); 2. To evaluate persistence of antibody and T-cell responses in a subset of these patients who were receiving ocrelizumab (OCR), other DMT or no DMT at the time of COVID-19 infection.

Background: Since March 2020, ˜15% of patients attending NYU MS Care Center (NYUMSCC) in New York City had COVID-19. It is unknown whether DMTs affect persistence of antibody and T-cell responses to SARS-CoV-2.

Design/Methods: Patients from NYUMSCC were invited to undergo serologic assessment using Elecsys Anti-SARS-CoV-2 (Roche Diagnostics) and multiplex bead–based immunoassays of antibody responses to SARS-CoV-2 nucleocapsid and spike proteins. A subset of patients with or without COVID-19 history underwent study of T-cell responses to SARS-CoV-2 spike protein using IFN-? enzyme-linked immunosorbent spot (Invitrogen) and TruCulture (Myriad RBM) spike protein assays and live virus immunofluorescence-based microneutralization assay.

Results: Since January 2021, 100 unvaccinated patients with MS were enrolled (mean 41 years; 63% female; 45% non-white; 35% on OCR; 26% had COVID-19). Antibody and T-cell results were available for 40 patients (26 on OCR; 17 had COVID-19, median 10 months before sampling). Of the 40, Elecsys Anti-

SARS-CoV-2 assay identified all but 2 COVID-19+ patients, and multiplex bead-based assay identified all but 1 COVID-19+ patient as seropositive. Neither assay had false positives. T-cell activation based on induced IFN-? secretion was observed in 10/17 COVID-19+ patients and 1 patient without COVID-19 history who developed PCR-confirmed COVID-19 five days after sampling. Anti-SARS-CoV-2 antibody response was detected in 4/5 and T-cell response in 3/5 OCR-treated COVID-19+ patients.

Conclusions: Preliminary results suggest persistent humoral and T-cell immune memory to SARS-CoV-2 up to 10 months following infection even in B-cell depleted patients with MS. Updated results will be presented.

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Comparison of Neurofilament Light and Total Tau as Blood-Based Biomarkers of Neurodegeneration: Associations with Cognition and Neuroimaging Outcomes

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Objective: We compared plasma total tau (T-tau) and neurofilament light (NfL) as cross-sectional and longitudinal markers of (1) global and domain-specific cognitive decline, and (2) neuroimaging markers of cortical thickness, hippocampal volume, white matter integrity, and white matter hyperintensity volume.

Background: Total tau protein and neurofilament light chain have emerged as candidate blood-based biomarkers of neurodegeneration. Studies have shown that cross-sectionally and longitudinally, elevated levels of plasma T-tau and NfL are associated with worse cognition and neuroimaging measures of cortical thickness, cortical atrophy, white matter hyperintensity, or white matter integrity. Studies have not compared how these biomarkers cross-sectionally or longitudinally associate with cognition and neuroimaging measures.

Design/Methods: We included 995 participants without dementia who were enrolled in the Mayo Clinic Study on Aging. All had concurrent plasma NfL and T-tau, cognitive status, and neuroimaging data. Follow-up was repeated approximately every 15 months for a median of 6.2 years. Plasma NfL and T-tau were measured on the Simoa HD-1 Platform. Linear mixed effects models adjusted for age, sex, and education examined associations between baseline z-scored plasma NfL or T-tau and cognitive or neuroimaging outcomes. Analyses were replicated in Alzheimer's Disease Neuroimaging Initiative (ADNI) among 387 participants without dementia followed for a median of 3.0 years.

Results: Baseline plasma NfL, compared to T-tau, was more strongly associated with cognitive and neuroimaging outcomes in all analyses. The combination of having both elevated NfL and T-tau at baseline, however, was more strongly associated at cross-section with worse global cognition and memory and with neuroimaging measures including temporal cortex thickness and increased number of infarcts. Longitudinally, T-tau did not add to the prognostic value of NfL. Analyses using ADNI had similar results.

Conclusions: Overall, plasma NfL had better utility as a prognostic marker of cognitive decline and neuroimaging changes. Plasma T-tau adds cross-sectional value to NfL in specific contexts.

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African American patients with MS/NMOSD have more rapid B-cell repopulation than white patients following infusion of anti-CD20 B-cell depleting therapy.

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Objective: To characterize and compare B-cell repopulation kinetics following anti-CD20 infusion in African American (AA) and white (WA) patients with multiple sclerosis (MS) or neuromyelitis optica spectrum disorder (NMOSD).

Background: Anti-CD20 therapies are highly effective in MS/NMOSD. Repopulation of B-cell subsets following anti-CD20 treatment has not been studied in AA who tend to have more severe disease.

Design/Methods: Demographics, disease-related information, and anti-CD20 treatment history were retrospectively collected on patients with MS or NMOSD who receive care at NYU MS Care Center and had flow cytometry results after infusion of rituximab or ocrelizumab. B-cell subsets (CD19, CD20, IgD, CD27 cluster analysis) from the date closest to infusion were analyzed with flow cytometry (BD FACSCanto™ and FACSCanto™ II Cell Analyzers). B-cell repopulation was defined as any detectable number of CD19+ cells on flow cytometry.

Results: Of 168 patients (134 MS, 32 NMOSD), 50 (29.8%) had detectable B-cell repopulation with a median of 6.8 months following anti-CD20 infusion. The ratio of B-cell subsets (%CD19+ cells) in patients with B-cell repopulation was as follows: 80.3%(±24.9%) IgD+/CD27-; 11.6%(±21.5%) IgD-/CD27+; 6.2%(±13.4%) IgD-/CD27-; 1.8%(±1.4%) IgD+/CD27+. B-cell repopulation was observed in no patients (0/40) <4 months following anti-CD20 infusion; 18/79 patients (23%) between 4-6 months; and 25/41 (61%) between 6-12 months following infusion. There was no difference in the frequency of B-cell repopulation between AA (5/24; 20.8%) and WA (5/28; 17.9%; p=0.79) 4-6 months following infusion, while 6-12 months after infusion, AA had a significantly higher frequency of B-cell repopulation (16/21;

76.2%) compared to WA (4/12; 33.3%; p=0.02). There were no differences in B-cell subset ratios in repopulated samples between AA and WA patients.

Conclusions: AA with MS/NMOSD had more rapid B-cell repopulation at 6-12 months following anti-CD20 infusion compared to WA, but similar relative distribution of B-cell subsets. This finding may have implications for clinical management of MS/NMOSD in AA.

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Neurological and Cardiac Improvements With PRX004 in Amyloidosis Patients: Results of a Phase 1 Study

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Objective: Evaluate the safety, pharmacokinetics (PK), and preliminary efficacy of PRX004 in hereditary amyloid transthyretin (hATTR) amyloidosis.

Background: hATTR amyloidosis is a rare, progressive, and fatal disease characterized by deposition of non-native transthyretin (TTR) protein aggregates in organs including the heart and peripheral nerves. Preclinically, PRX004 inhibited amyloid fibril formation, neutralized soluble aggregate forms of non-native TTR, and cleared insoluble amyloid fibrils through phagocytosis.

Design/Methods: Phase 1, open-label, dose-escalation (DE) study (dose cohorts: 0.1, 0.3, 1, 3, 10, and 30 mg/kg) with long-term extension (LTE); hATTR patients received PRX004 intravenously once every 28 days for up to 3 infusions in the DE phase and up to 15 infusions in the LTE phase.

Results: All 21 hATTR patients completed DE phase dosing; 17 patients enrolled in the LTE. No drug-related serious adverse events (AEs), drug-related =grade 3 events, deaths, or dose-limiting toxicities were reported. Most frequent AEs (=10%) were fall, anemia, upper respiratory tract infection, back pain, constipation, diarrhea, and insomnia. PRX004 demonstrated a PK profile consistent with IgG1 monoclonal antibodies. Based on PK/pharmacodynamic models, dose levels =3 mg/kg were predicted to enable clearance of >90% of amyloid deposits, thus dose cohorts 3, 10, and 30 mg/kg were considered equivalent, and efficacy assessments in these cohorts were pooled. At month 9, all 7 evaluable patient had slower progression versus natural history. (+1.29 vs +9). 3 of 7 patients demonstrated an improvement in Neuropathy Impairment Score (NIS) from baseline (mean change: −3.33).

Improvement in global longitudinal strain (GLS) was observed in all 7 patients (mean change: −1.21), and was further enhanced in the 3 patients with NIS improvement (mean change: –1.51). **Conclusions:** PRX004 was safe and well tolerated at all doses tested. Patients showed improvement/slower progression in neuropathy versus disease natural history and improvement in GLS, suggesting that amyloid targeting with PRX004 provides therapeutic benefit for patients.

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The effect of evobrutinib, a BTK inhibitor, on blood neurofilament light chain levels in relapsing multiple sclerosis

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Objective: To perform a post-hoc analysis of patients with relapsing multiple sclerosis (MS) in a phase II placebo-controlled trial, evaluating the effect of evobrutinib on blood neurofilament light chain (NfL) level, a biomarker of neuro-axonal damage in MS.

Background: Evobrutinib is a highly selective Bruton's tyrosine kinase inhibitor targeting B cells and myeloid cells. A phase II randomized trial (NCT02975349) in patients with relapsing MS showed evobrutinib reduced total T1 Gd+ lesions over 24 weeks vs placebo. The low annualized relapse rate observed up to week 48 was maintained in a long-term extension.

Design/Methods: Treatment groups were: placebo; evobrutinib 25mg once daily (QD); 75mg QD, 75mg twice daily (BID). NfL was measured blinded to treatment allocation in samples from baseline and weeks 4, 12, and 24 (Simoa NF-light™). The analysis population included all patients with NfL values at baseline and at least one post-baseline. A mixed model repeated measures (MMRM) model identified key variables from an extensive list of baseline covariates that significantly affected log(NfL) over time. The effect of evobrutinib vs placebo on log(NfL) over time was evaluated through MMRM modeling with adjustment for identified baseline covariates.

Results: Of 267 patients randomized, 166 (66%) were included in the NfL analysis population. Key selected baseline covariates were age, T2 lesion volume and Expanded Disability Status Scale score. Relative reductions of NfL levels by 18.9% (p=0.010) and 16.8% (p=0.040), respectively, were observed with evobrutinib 75mg BID vs placebo at weeks 12 and 24. For 75mg QD vs placebo at weeks 12 and 24,

relative reductions were 15.4% (p=0.043) and 14.1% (p=0.10, non-significant), respectively. No difference was observed with 25mg QD vs placebo.

Conclusions: Evobrutinib 75mg BID significantly lowers blood NfL levels as early as week 12, with reduced levels maintained until 24 weeks, indicating evobrutinib has a beneficial effect on reducing neuro-axonal damage in MS.

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Stroke complicating critically-ill patients with SARS-CoV-2: Analysis of the COVID-19 Critical Care Consortium (CCCC) international, multicentre observational study

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Objective: To determine the frequency, types and outcomes of stroke occurring as a complication of coronavirus disease 2019 (COVID-19) requiring intensive care unit (ICU) admission for acute respiratory distress syndrome (ARDS).

Background: COVID-19 has been implicated in the occurrence of neurological complications and associated increased morbidity and mortality. Cerebrovascular complications are particularly concerning, with a frequency from 1-6% reported in SARS-CoV-2 positive patients. However, such reports have generally been restricted to small patient populations and not specifically focussed on the most critically-ill patients requiring ICU care.

Design/Methods: The COVID-19 Critical Care Consortium (CCCC) is a prospective observational study enrolling patients over 18 requiring ICU admission for SARS-CoV-2 infection. Patients sustaining imaging-confirmed cerebrovascular events post ICU admission from January 1st through December 21st, 2020 were included in analysis. Survival models utilising parametric Weibull regression were used to investigate the impact of stroke on ICU death and discharge rates. These results were confirmed using semi-parametric Cox models.

Results: 2,715 eligible patients (median age=53, male=65%) were registered across more than 370 sites spanning 52 countries. Of these, 59 (2.2%) patients experienced acute stroke during their ICU stay: 19 (32%) ischemic, 27 (46%) haemorrhagic, and 13 (22%) unspecified. Haemorrhagic stroke greatly

increased the cumulative hazard of death (HR=4.99; 95% CI: 2.62, 9.52), while ischemic stroke did not (HR = 1.01; 95% CI: 0.43, 2.40). Despite high mortality (72%) in patients with haemorrhagic stroke, stroke was the primary cause of death in only 15%, with multiorgan failure the leading cause of death. The survival model demonstrated that the probability of having a stroke in the ICU was small, but gradually increased over time.

Conclusions: In an international registry of critically-ill COVID-19 patients, acute stroke was infrequent – occurring in just 2.2% of patients. Haemorrhagic, but not ischaemic stroke, was associated with significantly-increased mortality.

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Vagus Nerve Stimulation Paired with Upper Extremity Rehabilitation After Chronic Stroke: Cross-over results from the VNS-REHAB Pivotal Study

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Objective: To test the efficacy of Vagus Nerve Stimulation (VNS) paired with upper extremity rehabilitation after chronic stroke compared to rehabilitation paired with sham VNS.

Background: A recent randomized, blinded, controlled, trial of 108 people with upper extremity weakness at least 9 months after ischemic stroke, demonstrated significant improvements in impairment and function following rehabilitation paired with VNS compared to rehabilitation paired with sham VNS.

Design/Methods: Participants received 6 weeks of in-clinic intense rehabilitation followed by a 3-month home exercise program that marked the conclusion of blinded follow-up. Thereafter, sham VNS participants crossed over to receive 6 weeks of VNS-paired in-clinic rehabilitation (n=47) followed by a 3-month home exercise program (n=41). The results of this crossover phase are presented here and full statistical analysis will be available for the meeting. Fugl-Meyer Upper Extremity (FMA-UE, primary outcome) and Wolf-Motor Function Test (WMFT) scores were assessed pre-randomization, after sham VNS and then again after crossover.

Results: During sham VNS, participants' FMA-UE score increased from 35.6 (SD 8.1) at baseline to 38.7 (SD 9.8) after the home exercise period. Following crossover to active VNS + rehabilitation, the FMA-UE score increased further to 41.6 (SD 9.8). It was 40.9 (SD 10.6) after the home exercise period. During

sham VNS, participants' WMFT score increased by 0.4 points (SD 0.5). During active VNS, the WMFT score increased by a further 0.2 points (SD 0.4). Ten (24%) and 14 (34%) people exceeded the minimal clinically important difference for FMA-UE (= 6 points) and WMFT (= 0.4 points) respectively following active VNS. No related adverse or serious adverse events were reported during crossover.

Conclusions: Participants who initially received sham VNS + rehabilitation exhibited further improvements once they received a course of active VNS paired with rehabilitation. Overall, these participants experienced similar improvements to those who were initially randomized to active VNS group.

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Neurologic and radiographic findings associated with Paediatric Inflammatory Multisystem Syndrome Temporally associated with SARS-CoV-2 (PIMS-TS) in Children

Omar Abdel-Mannan, MD, Justin Penner, Jane Hassell, Imke Meyer-Parsonson, Ulrike Loebel, Zoe Berger, Lesley Cavalli, Sue Maillard, Ronit Pressler, Mae Johnson, Alasdair Bamford, Karyn Moshal, Yael Hacohen, MBBS

Objective: Our aim was to report neurological manifestations of children with Paediatric Inflammatory Multisystem Syndrome Temporally associated with SARS-CoV-2 (PIMS-TS)

Background: Neurological manifestations have been reported both in adults and children with coronavirus disease 2019 (COVID-19). Paediatric Inflammatory Multisystem Syndrome Temporally associated with SARS-CoV-2 (PIMS-TS) is a recently described severe post-infectious immune-mediated disorder.

Design/Methods: Patients (<18yrs) presenting to Great Ormond Street Hospital between March 1, 2020, and June 21, 2020 fulfilling PIMS-TS criteria, were included. Clinical and paraclinical features were retrieved retrospectively from electronic patient records.

Results: Data was available for 45 patients who presented during the study period. Median age was 10.1 years (IQR 8.8, 13.5), 29 (64.4%) were male and 37 (82.2%) were of non-white ethnicities. New-onset neurological symptoms were reported in 23/45 (51.1%); headaches (n=16), encephalopathy (n=7), dysarthria/dysphonia (n=6), hallucinations (n=4), ataxia (n=4), peripheral nerve involvement (n=3), and seizures (n=1). One patient had 118 leukocytes in CSF. Splenium signal changes were seen in all 4/14 patients on brain MRI. A mild excess of slow activity was found in 10/10 who had an EEG and mild myopathic and neuropathic changes were seen 4/5 who underwent nerve conduction studies and

electromyography. Children with neurological involvement had higher peak inflammatory markers and were more likely to be ventilated and require inotropic support in PICU ($p<0.05$).

Conclusions: Children with PIMS-TS presented with new neurological symptoms involving both the central and peripheral nervous systems, in the absence of respiratory symptoms. Neurological symptoms were seen more frequently in more severe presentations.

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Association of COVID-19 infections with novel and breakthrough epileptic seizures

Hardik Bhaskar, Neeraj Singh, MD

Objective: This study explores the relationship between the incidences of COVID-19 infections and novel or breakthrough epileptic seizures in the largest patient sample to date in a single New York-based hospital system.

Background: Since the advent of the COVID-19 pandemic, anecdotal reports have indicated a possible relationship between COVID-19 infections and novel seizures. We analyzed 534 patients who were admitted with COVID-19 infections and administered antiepileptic medications between 1 February and 30 June 2020 within a single health system in New York City and adjacent counties.

Design/Methods: Patients were included in this case control study if they were admitted to a hospital in the health system and had a confirmed positive test for COVID-19 infection during the admission. Only patients who were administered antiepileptic medications during the admission for any reason were included in this study. These patients were divided into those with and those without a known history of epilepsy. The incidences of new-onset seizures and mortality rates were compared between these groups using Pearson's chi-squared test, and then statistical significance with Fisher's exact test and odds ratios (OR) were calculated.

Results: Novel seizures were more likely to occur in patients without a known history of epilepsy than in patients with one ($p<0.0001$, OR=2.65). Mortality rates were higher among patients who had a novel seizure than those who did not ($p=0.0250$, OR=1.70). There was no difference in mortality rates between patients who had a history of epilepsy and those who did not ($p=0.6632$).

Conclusions: These results reveal a higher incidence of new-onset seizures in patients without a known history of epilepsy than the incidence of breakthrough seizures in patients with a known history of

epilepsy. This may indicate that new COVID-19 infections could cause novel seizures in patients without pre-existing epilepsy, and would warrant further exploration into the pathophysiology of this phenomenon.

Study Supported By:

None

Disclosures:

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Optimization of AOC-1001, an antibody-oligonucleotide conjugate targeting the underlying cause of myotonic dystrophy type 1

Rob S. Burke, Barbora Malecova, Philip Kovach, Michael D. Hood, Samuel W. Beppler, Ramana Doppalapudi, Michael Cochran, Gulin Erdogan, Danny Arias, Christopher D. Miller, David Sala, Beatrice Darimont, Rachel Johns, Anneke K. Raney, Andrew J. Geall, Elizabeth J. Ackermann, Sole Gatto, Adam Pavlicek, Vivienne Bunker, Eve Duchemin-Pelletier, Oana Lorintiu, Joanne Young, Markus Hossbach, Martin Koegler, Lukas Perkams, Philipp Hadwiger, Arthur A. Levin

Objective: To develop therapy for Myotonic Dystrophy Type 1 (DM1), a rare, progressive neuromuscular disease with no approved therapy, that arises from CTG repeat expansions in the DMPK gene.

Background: The toxic gain-of-function DMPK mRNA can be targeted with oligonucleotides for degradation. Delivery of oligonucleotides into muscle has been limited. Antibody-Oligonucleotide Conjugates (AOCs) represents a new class of therapeutics allowing delivery of oligonucleotides to target tissues.

Design/Methods: We conducted biochemical and cell-based studies with the lead DMPK siRNA, as well as pharmacological evaluation of the clinical candidate AOC1001 in non-human primates.

Results: Cell fractionation of DM1 patient-derived cells treated with siDMPK.19 demonstrated a reduction of DMPK mRNA levels in nucleus (60%) and cytoplasm (80%). Immunofluorescent analysis showed reduction of DM1-associated nuclear foci by 50% in the myotubes cultured from DM1 patients treated with siDMPK.19. Treatment with siDMPK.19 corrected the aberrant splicing (56.5% correction of splicing signature) in myotubes obtained from DM1 patient. In vivo experiments in non-human primates demonstrated excellent activity of DMPK-targeted AOC1001, composed of monoclonal antibody targeting transferrin receptor (TFRC) and DMPK siRNA, in muscle. A single intravenous (IV) infusion of

AOC1001 at 0.6, 2, or 6 mg/kg (siRNA dose) produced a dose-dependent reduction in DMPK expression in the quadriceps, gastrocnemius, and tibialis anterior muscles with an ED50 < 1 mg/kg. Following a single IV dose of AOC1001 at 2 mg/kg (siRNA dose), the approximately 75% reduction in DMPK mRNA levels was sustained up to three months post-dose in quadriceps and gastrocnemius. Four weeks after a single IV administration of AOC1001 at 6 mg/kg (siRNA dose), substantial reduction (about 75% or more) of DMPK mRNA was observed in heart and in a large variety of skeletal muscle assessed, including the intercostals and diaphragm.

Conclusions: Based on these data, clinical investigation of AOC1001 in DM1 patients is planned.

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Leriglitazone Improved Progression of Myelopathy-related Symptoms, and Reduced Cerebral Lesions in Patients with Adrenomyeloneuropathy in a Phase 2/3 Clinical Study

Reza Seyedsadjadi, MD, Florian Eichler, MD, Jacinda B. Sampson, MD, PhD, Ettore Salsano, MD, Josep Gamez, MD, PhD, Silvia Pascual, Guillem Pina, Maria Pascual, PhD, Marc Martinell

Objective: Efficacy of leriglitazone (MIN-102) on the progression of adrenomyeloneuropathy (AMN)

Background: Leriglitazone is a brain penetrant peroxisome proliferator-activated receptor γ (PPARγ) agonist.

Design/Methods: 2-year, placebo-controlled study in adult male patients with 2:1 randomization. Primary endpoint: 6-minute walk test (6MWT). Secondary endpoints: body sway amplitude, Severity Score System for Progressive Myelopathy (SSPROM), Expanded Disability Status Scale (EDSS), Clinician- and Patient Global Impressions of Improvement (CGI-I, PGI-I). Serial MRIs were rated by investigators and 2 independent central readers blinded to treatment for progression of cerebral lesions. Exploratory endpoint: neurofilament light (NfL) plasma levels.

Results: 116 patients were randomized (77 leriglitazone, 39 placebo). 96 patients completed double-blind treatment. 6MWT did not meet the primary endpoint in the overall population likely due to long disease history (mean 11.3 yrs.) resulting in plateauing of decline. In body sway, leriglitazone showed statistically significant differences vs. placebo in ‘eyes closed, feet together' in sway total and mediolateral amplitude (p=0.036 and p=0.003, respectively; ANCOVA), and anteroposterior amplitude in “eyes close, feet apart” (p=0.004, ANCOVA). Leriglitazone consistently showed favourable results in CGI-I, EDSS and SSPROM with p values Edema and weight gain were the most frequently reported adverse events. Treatment discontinuation rate for adverse events was low (10.4% leriglitazone vs. 5.1 placebo).

Conclusions: Leriglitazone had a favorable safety profile, improved postural control and reduced risk of developing of cerebral lesions.

Study Supported By:

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FINTEPLA (Fenfluramine) Treatment Improves Everyday Executive Functioning in Patients With Lennox-Gastaut Syndrome: Analysis From a Phase 3 Clinical Trial

Kim I. Bishop, PhD, Gerard A. Gioia, MD, Ingrid E. Scheffer, AO, MBBS, PhD, FRACP, Gail M. Farfel, PhD, Arnold Gammaitoni, Pharm.D

Objective: To determine whether fenfluramine (Fintepla®) improves everyday executive function in a randomized clinical trial (RCT) of patients with Lennox-Gastaut syndrome (LGS), a developmental and epileptic encephalopathy characterized by profound cognitive and neurodevelopmental impairment.
Background: Adjunctive fenfluramine improved seizure control and everyday executive function in patients with Dravet syndrome; fenfluramine reduced frequencies of drop seizures and generalized tonic-clonic seizures in a recent LGS RCT.
Design/Methods: Patients with LGS received placebo or fenfluramine (0.2 or 0.7 mg/kg/day) for 14 weeks. Executive function was evaluated at baseline and Week 14 for patients aged 5-18 years with the Behavior Rating Inventory of Executive Function (BRIEF®) parent form; items were mapped to the updated BRIEF®2 (Behavior Regulation Index, BRI; Emotion Regulation Index, ERI; Cognitive Regulation Index, CRI; and Global Executive Composite, GEC). Clinically meaningful worsening in BRIEF®2 indexes/composite T-scores from baseline to Week 14 was defined as exceeding a Reliable Change Index (RCI) of =80% certainty. Clinically meaningful improvement was defined using a more stringent RCI =95% certainty. Active vs placebo treatment groups were compared statistically using Somers' D.
Results: Data were analyzed for 137 evaluable patients (placebo, n=45; fenfluramine, n=92; median age, 12-13 years; 53% male). Median T-scores at baseline were in the clinically elevated range (T=65) for BRI, CRI, and GEC (T=66, 65, and 67, respectively; ranges 35-90). Treatment with fenfluramine was associated with no significant worsening in any of the BRIEF®2 indexes/composite T-scores compared to placebo (p>0.05; RCI=80%). Treatment with fenfluramine was associated with significant and clinically meaningful improvements in CRI (27% vs 13%, p=0.046) and GEC (25% vs 11%; p=0.034) vs placebo (RCI>95%).
Conclusions: In an LGS RCT population with a high frequency of executive function impairment at baseline, parents of ~25% of children treated with fenfluramine for 14 weeks observed clinically meaningful improvement in CRI and GEC.

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