



## 2024 Annual Meeting Emerging Science Abstracts

Abstracts qualify for Emerging Science presentations by having key aspects of research conducted after the October abstract submission deadline and must be new and of sufficient scientific importance to warrant expedited presentation and publication. These previously unpublished abstracts contain timely, significant, and innovative content.

Experts rate the abstracts on scientific merit, breadth of audience interest, and quality of presentation, including compliance with the guidelines and instruction.

### Primary and Secondary Results of LUMINESCE, a Phase 3 Study of Interleukin-6 Signaling Inhibition by Satralizumab in Generalized Myasthenia Gravis

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**Objective:** To report primary and notable secondary efficacy and safety results of LUMINESCE (NCT04963270), a Phase 3 study investigating satralizumab in patients aged  $\geq 12$  years with generalized myasthenia gravis (gMG).

**Background:** gMG, a rare autoimmune disease affecting the neuromuscular junction, results in fatigable skeletal muscle weakness. Pre-clinical and clinical data implicate IL-6 in the pathology of MG, suggesting its therapeutic target viability. Satralizumab, a humanized IL-6 receptor monoclonal recycling antibody, provides durable inhibition of IL-6 signaling, which has the potential to modulate upstream immunopathogenic mechanisms in gMG. Satralizumab is approved for the treatment of anti-aquaporin-4-seropositive neuromyelitis optica spectrum disorder, with long-term (~9 years) experience regarding its benefit:risk profile. This is the first report of data assessing IL-6 signaling inhibition with satralizumab in gMG, and will inform on the benefit:risk profile of satralizumab in gMG.

**Design/Methods:** Eligibility criteria included gMG seropositivity (AChR-IgG+, MuSK-IgG+, or LRP4-IgG+), an MGFA severity class II–IV, an MG-ADL score  $\geq 5$  (non-ocular contribution  $>50\%$ ), and use of stable background therapy. Participants were randomized 1:1 to receive subcutaneous satralizumab or placebo at Weeks 0, 2, 4, and Q4W thereafter until Week 24. The primary efficacy endpoint was mean



change from baseline in total MG-ADL score at Week 24 (AChR-IgG+). Secondary efficacy endpoints include, but are not limited to, mean change from baseline in QMG score, percentage of patients with  $\geq 2$  points reduction in total MG-ADL score, and percentage of patients with  $\geq 3$  points reduction in QMG score, at Week 24 (AChR-IgG+); and durability of efficacy of satralizumab. Safety analyses included incidence and severity of adverse events.

**Results:** To date, 186 participants were randomized. Baseline demographics, and primary and notable secondary efficacy and safety results will be presented.

**Conclusions:** LUMINESCE, the first study of IL-6 signaling inhibition with satralizumab in gMG, will generate important data to evaluate satralizumab's efficacy and safety in gMG.



## **PrimeC, An Oral Candidate for Amyotrophic Lateral Sclerosis, Meets Primary Safety and Secondary End Points in the Phase 2b PARADIGM Trial**

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**Objective:** Assess the safety, tolerability and efficacy of PrimeC in patients with amyotrophic lateral sclerosis (ALS) in a randomized, placebo-controlled, double-blind, multi-centered Phase 2b trial (PARADIGM; NCT05357950).

**Background:** ALS is a complex disease with multiple pathological mechanisms requiring multi-factorial therapeutic approaches. PrimeC, a unique formulation of ciprofloxacin and celecoxib, is designed to synergistically target several key pathological mechanisms of ALS. In a previous Phase 2a trial, PrimeC demonstrated a favorable safety profile and trends toward slowing progression of functional and respiratory decline in ALS patients.

**Design/Methods:** 69 participants were randomly assigned to receive PrimeC or placebo in a 2:1 ratio for 6 months. One patient was misdiagnosed with ALS and was excluded from the pre-defined analysis. Upon completion of the initial 6 months, participants were enrolled into a 12-month open-label-extension, during which all were administered with PrimeC, blinded for the original treatment allocation. Safety, ALSFRS-R, SVC, QoL, ALS associated biomarkers and survival were collected during the trial.

**Results:** Safety outcomes did not differ significantly between treatment arms. In an Intended-To-Treat (ITT) analysis (n=68), the difference in the adjusted ALSFRS-R score between arms at 6 months was 29.2% (0.37 difference points/month; 95% CI, -0.1 to 0.84; p=0.12). In a Per-Protocol (PP) analysis (n=62), the mean rate of change was -0.9 points/month with PrimeC and -1.43 points/month with placebo (0.53 difference points/month; 95% CI, 0.05 to 1.01; p=0.03), showing a statistically significant difference of 37.4% between the two arms in 6-months of treatment. The adjusted SVC mean revealed a difference of 17.2% (p=0.39) in the PP dataset and 13.3% (p=0.5) in the ITT dataset.

**Conclusions:** These findings indicate that PrimeC is safe and may have a meaningful positive impact on ALS clinical outcomes. The data supports moving forward to a Phase 3 pivotal trial. Further analysis of biomarkers may provide additional support to the clinical results.



## **Efficacy and Safety of Bexicaserin (LP352) in Adolescent and Adult Patients with Developmental and Epileptic Encephalopathies (DEEs): Results of the Phase 1b/2a PACIFIC Study**

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**Objective:** To assess safety, tolerability, pharmacokinetics, and efficacy of bexicaserin (LP352) for treatment of seizures in developmental and epileptic encephalopathies (DEEs).

**Background:** DEEs are the most severe group of epilepsies characterized by drug-resistant seizures, epileptiform abnormalities, and developmental slowing or regression. DEE trials have focused on patients with specific epilepsy syndromes such as Dravet syndrome (DS), Tuberous Sclerosis Complex, and Lennox-Gastaut Syndrome (LGS), the latter has etiological heterogeneity. Here, we present a novel Phase 1b/2a study of patients with DEEs treated with bexicaserin, a potent and highly selective 5-HT<sub>2C</sub> receptor superagonist.

**Design/Methods:** The PACIFIC study investigated the safety, tolerability, pharmacokinetics, and efficacy of bexicaserin for seizure treatment in patients aged 12-65 years with DEEs (DS, LGS, and DEE Other). Patients were randomized (4:1) to bexicaserin or placebo and underwent a 15-day flexible titration period (maximum dose of 12 mg TID, based on tolerability), followed by 60 days of maintenance, and a 5- to 15-day taper. Key inclusion criteria included  $\geq 4$  countable motor seizures during 28-day screening and  $\leq 4$  concomitant antiseizure medications. Key exclusion criteria included use of fenfluramine. No echocardiogram monitoring was performed.

**Results:** 52 patients (43 bexicaserin, 9 placebo) were enrolled (29 LGS, 4 DS, and 19 DEE Other) across 34 sites. 35 patients took bexicaserin in the full analysis set, with 30 (85.7%) achieving maximum dosing. Most common adverse events were somnolence, decreased appetite, constipation, and diarrhea. Median countable motor seizure reduction with bexicaserin was 59.8% versus 17.4% with placebo. Median motor seizure reduction in DS was 74.6% (no placebo comparator), LGS 50.8% (placebo: 17.4%), and DEE Other 65.5% (placebo: 32.2%).

**Conclusions:** Bexicaserin exhibited a favorable safety and tolerability profile in this study. Efficacy as assessed by seizure reduction was similar in all subgroups, including LGS and DEE Other, which are highly etiologically heterogeneous disorders.



## **Clinical utility of synuclein skin biopsy in the initial diagnosis and evaluation of parkinsonian disorders**

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**Objective:** To determine the clinical utility of phosphorylated alpha-synuclein (P-SYN) within skin biopsies in diagnostic and management decisions.

**Background:** The initial diagnosis of Parkinson's Disease (PD) and related parkinsonian disorders is primarily made clinically, but may be incorrect in up to 25% of patients. Diagnostic accuracy increases with time after initial diagnosis as clinical features and red flags pointing to other disorders emerge. The need for earlier and accurate diagnosis of these progressive neurodegenerative disorders is a major unmet need impacting diagnostic certainty, early symptomatic treatment, and avoidance of inappropriate therapy. Cutaneous nerves in skin biopsies can be stained for PSYN, which is a diagnostic biomarker for degenerative synucleinopathies, including PD, multiple system atrophy and dementia with Lewy bodies.

**Design/Methods:** Retrospective chart review of consecutive patients with suspected parkinsonism seen in the Beth Israel Deaconess Medical Center Department of Neurology from 2021- 2023 who received a skin biopsy for P-SYN as part of their clinical evaluation. Changes to the clinical diagnosis and treatment were assessed after P-SYN biopsy results.

**Results:** Ninety-Seven consecutive patients were identified and reviewed. Overall, 66% had a change in diagnosis, 55% had a change in treatment, and 34% had a diagnosis confirmed. We identified several common clinical scenarios in which the test led to changes in diagnosis and/or management: PD with unclear levodopa response, idiopathic PD vs. drug induced PD, prominent action tremor (PD vs. essential tremor), lower extremity predominant PD, autonomic predominant PD, memory disorder predominant PD, and early subtle signs of PD. Changes in treatment followed clarification of clinical diagnosis and whether phosphorylated alpha synuclein was identified on skin biopsy.

**Conclusions:** Skin biopsy for phosphorylated alpha synuclein can improve clinical diagnosis and impact treatment when a diagnosis of parkinsonism is uncertain.





## Impact of Deep Brain Stimulation on Human Cognition Depends on Age and Subiculum-Retrosplenial Cortex Connectivity

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**Objective:** To understand how electrode connectivity and patient age influence cognitive outcomes of deep brain stimulation (DBS) across Parkinson Disease (PD) and Alzheimer Disease (AD).

**Background:** Recent research has demonstrated that brain lesions and DBS electrodes functionally connected to the subiculum-retrosplenial cortex (SBC-RSC) impair cognition. However, other research has demonstrated what seems to be the opposite effect in AD DBS.

**Design/Methods:** We studied electrode locations and cognitive outcomes in who received subthalamic nucleus deep brain stimulation for PD (N = 33) and fornix deep brain stimulation for AD (N = 46). We related DBS sites to the lesion-based a-priori SBC-RSC region of interest. We tested whether connectivity between DBS sites and the SBC-RSC was significantly correlated with memory outcomes, and whether the difference between PD and AD was significant. We then used whole brain mapping to assess if both diseases were driven by the same region in the SBC-RSC. Finally, we investigated the influence of patient age upon outcome.

**Results:** Connectivity to the SBC-RSC was simultaneously correlated with cognitive decline in PD and cognitive improvement in AD. The difference between the two diseases was statistically significant. Whole-brain data-driven analysis of connections correlating with cognitive decline revealed both diseases were driven by the same SBC-RSC region. Subsequent regression analysis demonstrated both groups interacted significantly with patient age. High SBC-RSC connectivity improved older patients but impaired younger patients. Low SBC-RSC connectivity had the opposite effect on the age groups. Data-driven analysis identified the inflection point occurred at 65 in both diseases.

**Conclusions:** The cognitive effects of DBS in PD and AD are unified by considering connectivity to the SBC-RSC and patient age. The magnitude of the impact upon cognition primarily correlates with the degree of deep brain stimulation connectivity to the SBC-RSC. However, whether DBS impairs or improves cognition depends upon patient age.



## Long-Term Safety, Tolerability, and Efficacy of Atogepant for the Preventive Treatment of Migraine: Interim Analysis of a Phase 3, Multicenter, Open-Label, 156-Week Long-Term Safety Extension Study

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**Objective:** Evaluate the long-term safety and efficacy of atogepant for the preventive treatment of migraine.

**Background:** Atogepant is an oral calcitonin gene-related peptide receptor antagonist approved for the preventive treatment of migraine. ELEVATE and PROGRESS were phase 3, randomized, doubleblind, placebo-controlled trials evaluating atogepant for the preventive treatment of episodic migraine (EM) in participants with an inadequate response to 2–4 classes of conventional oral preventive treatment (ELEVATE), and for the preventive treatment of chronic migraine (CM) (PROGRESS).

**Design/Methods:** This interim analysis (September 14, 2023) of the open-label, 156-week, long-term safety extension study evaluated atogepant 60 mg once daily for the preventive treatment of EM or CM in participants who completed ELEVATE or PROGRESS, respectively. The long-term safety, tolerability, and efficacy of atogepant in participants completing Week 48 or early termination was evaluated. Efficacy was assessed during the first 48 weeks.

**Results:** The safety population in this interim analysis included 595 participants (ELEVATE, n=270; PROGRESS, n=325). Mean duration of atogepant exposure was 496.5 days. Treatment-emergent adverse events (TEAEs) occurred in 79.0% of participants; most were mild/moderate and not related to atogepant. Common TEAEs (≥5%) were COVID-19 (28.7%), nasopharyngitis (10.9%), and constipation (8.2%). One death attributed to asphyxia by housefire was observed. Other serious TEAEs occurred in 5.5% of participants and were not related to atogepant. TEAEs leading to discontinuation occurred in 5.9% of participants. ALT/AST ≥3 x ULN occurred in 2 participants; none met Hy's Law. Least square mean change from baseline in monthly migraine days was -5.5 (ELEVATE) and -10.9 (PROGRESS) at Weeks 13-16 and was sustained over 48 weeks. Similar outcomes were observed for monthly headache days and monthly acute medication use days.

**Conclusions:** The overall safety results were consistent with the known safety profile of atogepant. No new safety signals were identified. Improvements in efficacy outcomes were sustained over 48 weeks.



## Initial Data from the DELIVER Trial of DYNE-251 in Males with DMD Mutations Amenable to Exon 51 Skipping

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**Objective:** Determine the safety and efficacy of DYNE-251 in ambulant and non-ambulant males aged 4-16 with DMD mutations amenable to exon 51 skipping (Phase 1/2 DELIVER trial, NCT05524883).

**Background:** Duchenne muscular dystrophy (DMD) is caused by absence of functional dystrophin protein. Approved PMO therapies induce exon skipping to restore the DMD mRNA reading frame leading to the production of truncated, functional dystrophin, but their potential is limited by poor muscle delivery. DYNE-251, an investigational therapeutic for DMD, consists of an exon 51-skipping PMO conjugated to a TfR1-targeting Fab to deliver increased levels of PMO to muscles.

**Design/Methods:** In the MAD portion of DELIVER, participants are randomized to receive DYNE-251 or placebo Q4W for 6 months across 7 PMO dose levels up to 40 mg/kg. For analysis of exon skipping and dystrophin data from the 5 mg/kg cohort, 4 participants received DYNE-251 and 2 received placebo. Safety and tolerability are based on 37 participants enrolled in DELIVER as of the data cutoff date.

**Results:** At 6 months, 5 mg/kg DYNE-251 showed a mean 657 ng/g PMO concentration in muscle and mean absolute exon skipping level of 0.90% (0.80% difference from baseline). Mean absolute dystrophin level, measured by Western blot, increased from 0.60% at baseline to 0.88% of normal at 6 months, and the mean level of dystrophin positive fibers (PDPF) increased from 2.4% at baseline to 22.2% at 6 months. As of the data cut-off date, DYNE-251 demonstrated a favorable safety profile with mostly mild or moderate TEAEs. There was no treatment-emergent anemia or clinically meaningful changes in kidney parameters or electrolytes.

**Conclusions:** Based on these initial data, DYNE-251 had a favorable safety profile and reached levels of dystrophin expression, exon skipping, and PDPF at 6 months that exceeded levels reported at the same time point in prior clinical trials evaluating the standard of care PMO.





## **Limbic Posterior, Peri-Central, and Paralimbic Cortical Cholinergic Losses Predict Cognitive Changes in Parkinson Disease: A Two-Year**

Longitudinal [18F]-FEOBV PET Study

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**Objective:** To apply statistical parametric mapping (SPM) whole brain voxel-based analysis of [18F]-fluoroethoxybenzovesamicol (FEOBV) vesicular acetylcholine transporter (VACHT) brain PET to predict 2-year cognitive changes in Parkinson disease (PD).

**Background:** Dementia is a debilitating non-motor complication of PD affecting most patients with advancing disease. Post-mortem studies revealed prominent cholinergic neuron loss in the basal forebrain in PD patients with dementia. Cross-sectional brain imaging studies showed evidence of prominent cholinergic terminal deficits in posterior cortical brain regions in non-demented patients. Longitudinal studies are sparse, small in sample size, and use less specific proxy cholinergic markers not directly targeting nerve terminals. VACHT PET ligands are spatially resolute and allow reliable quantification in high-binding areas of the brain compared to prior generation PET ligands.

**Design/Methods:** 77 PD participants underwent baseline brain VACHT [18F]-FEOBV PET, MRI imaging and completed a comprehensive neuropsychological test battery at baseline and at two-year follow up. Percent differences between baseline and follow-up global composite cognitive Z-scores were used to identify longitudinal cognitive changes, with negative scores indicating decline and positive scores indicating no evidence of decline. SPM12 whole brain voxel-regression analysis was performed to identify statistically significant clusters of spatially contiguous voxels correlating with global cognitive decline.

**Results:** Our analysis showed baseline reduced VACHT binding of the mid to posterior cingulum, precuneus, parietal-lateral occipital, right more the left superior temporal, insula, opercular, right more than left precentral and postcentral gyrus, and insulae (cluster-FDR adjusted significant at  $p < 0.05$ ) predicting cognitive decline.

**Conclusions:** This is the first longitudinal, large scale cholinergic PET study showing that limbic posterior brain (cingulum), peri-central cortices, and paralimbic cortices are an early predictor of cognitive decline in PD. These findings may augur novel studies targeting specific posterior limbic, primary sensorimotor and paralimbic circuitry to treat cognitive decline in PD.



## **Safety, Pulmonary Function, and Motor Function in Ambulatory and Nonambulatory Participants With Duchenne Muscular Dystrophy Treated With Viltolarsen: Results From the Galactic53 Clinical Trial**

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**Objective:** To evaluate safety, motor function, and respiratory function, including forced vital capacity (FVC) and peak expiratory flow (PEF), in participants with Duchenne muscular dystrophy (DMD) and treated with viltolarsen.

**Background:** Decline in pulmonary function is a concern for DMD patients. Viltolarsen is indicated for the treatment of DMD patients with dystrophin mutations amenable to exon 53 skipping. In previous studies, viltolarsen increased dystrophin levels, stabilized motor function over 4 years, and was well-tolerated. Pulmonary function was not evaluated previously.

**Design/Methods:** This Phase 2, 48-week study evaluated safety and motor and pulmonary function in ambulatory and nonambulatory participants with DMD aged  $\geq 8$  years treated with viltolarsen 80 mg/kg/week (NCT04956289). Percent predicted FVC (FVC%p) and percent predicted PEF (PEF%p) in viltolarsen-treated participants was compared with participants from the Cooperative International Neuromuscular Research Group Duchenne Natural History Study (DNHS cohort), which was matched for age and ambulatory, pulmonary, and steroid status.

**Results:** The mean age of viltolarsen-treated participants (N=20) was  $12.8 \pm 5.47$  years; 50% were nonambulatory. The mean age of the DNHS cohort (N=48) was  $12.7 \pm 4.05$  years; 48% were nonambulatory. In the safety population, 19 viltolarsen-treated participants reported a treatment-emergent AE; 4 events were assessed as drug-related. No serious AEs or deaths were reported. No participants discontinued. Mean change from baseline in FVC%p and PEF%p for viltolarsen-treated participants ( $5.15 \pm 2.3$  and  $5.0 \pm 3.7$ , respectively) was significantly improved at Week 49 compared to DNHS cohort ( $-0.93 \pm 1.5$ ;  $P=0.03$  and  $-6.0 \pm 2.4$ ;  $P=0.02$ , respectively). Performance of Upper Limb 2.0 was stable over the treatment period.

**Conclusions:** Safety of viltolarsen treatment is consistent with previous trials. In this first study examining viltolarsen effects on pulmonary function, the data indicate a positive effect on FVC and PEF, and combined with previous motor function data, suggests an additional treatment benefit of viltolarsen for DMD patients amenable to exon 53 skipping therapy.



## Impact of Automated Seizure-Burden Measurements on Functional Outcomes: Sub-Analysis of SAFER-EEG Trial

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**Objective:** To determine the association of seizure burden (SzB), estimated with an automated machine-learning algorithm, with functional outcomes.

**Background:** Recent studies have shown associations between severe epileptiform activity and poor functional outcomes (Parikh, et al., 2023). These studies used continuous electroencephalography (EEG), which is not widely available. Clarity is a machine learning algorithm that monitors SzB and alerts of suspected status epilepticus (SE) (Kamoussi, et al, 2021) using point-of-care (POC)- EEG recordings. We pose that higher SzB will be associated with poor outcomes, measured by modified Rankin scale (mRS) score and long-term care facility (LTCF) discharge.

**Design/Methods:** A sub-analysis on data from the retrospective SAFER-EEG trial, on cases from the POC-EEG cohorts. Clarity was run post-hoc in the POC-EEGs, and outputted the maximum 5-min SzB per hour, in non-overlapping bins. We analyzed outcomes in patients with a max. SzB  $\geq 50\%$  towards the end of the recording, including those with a suspected SE alarm (SzB  $\geq 90\%$ ).

**Results:** From 344 POC-EEG cases, 178 (52%) had SzB of zero throughout the recording and 41 (12%) had suspected SE. We found that patients that had a max. SzB  $\geq 50\%$  in the last quarter of the recording (N = 31) were more likely to have unfavorable mRS outcomes compared to those without any seizure activity (77% vs. 57%,  $p = 0.035$ ). Moreover, in a sub-analysis of the patients with SE alarm (N = 17), the proportion with poor functional outcomes was higher (82%,  $p = 0.044$ ). In the survivors group (N = 268), we found that a higher proportion of patients with SzB  $\geq 50\%$  towards the end of the recording (N = 24) were discharged to LTCF (79% vs. 54%,  $p = 0.02$ ).

**Conclusions:** For the first time, we report associations between poor functional outcomes and sustained seizure activity, as measured through an automated seizure-burden monitoring algorithm.



### Results of the ARCADIA-CSI Cognition Study

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**Objective:** To determine if apixaban prevents cognitive decline in patients with cryptogenic stroke (CS) and atrial cardiopathy (AC).

**Background:** The ARCADIA trial (n=1015), a secondary stroke prevention study, evaluated the efficacy of apixaban vs aspirin in patients with CS and AC. We hypothesized that the rate of neurocognitive decline would be slower among subjects randomized to apixaban due to fewer silent infarcts.

**Design/Methods:** Subjects randomized in ARCADIA who were actively taking study drug were approached for enrollment into this ancillary study. Participants underwent serial neurocognitive testing administered centrally by telephone. The baseline was obtained >3 months after the index stroke and follow-up yearly thereafter. Testing consisted of a 5-test battery and patients' overall cognitive functioning was summarized as a composite Z-score based on scores from the five tests. Patients with a baseline composite Z-score > 1.5 SDs below norms were excluded from the analyses. Trajectories of the composite Z-score and on each individual test were compared between treatment arms using a mixed-effect model.

**Results:** Of the 310 enrolled in ARCADIA-CSI, 14 (5%) did not complete any neurocognitive batteries. Of the 296 subjects with baseline data, 47 (16%) were excluded due to impaired baseline scores. In the remaining 249 patients (apixaban 128, aspirin 121), 582 cognitive assessments were obtained. Baseline characteristics were balanced between the apixaban and aspirin arms. Mean age was 66.7 years, median mRS 1, 52% female and 19% black patients. During median follow-up of 378 days, the annual change in the overall standardized composite score was similar in the aspirin arm (0.08; 95% CI:0.02-0.15) and the apixaban arm (0.11; 95% CI:0.04-0.17). There were also no differences between treatment arms when comparing cognitive trajectories of each individual neurocognitive test.

**Conclusions:** Among patients with CS and AC, the rate of cognitive change was not improved with apixaban compared to aspirin.



## Evidence of Target Engagement in a Phase 1 Clinical Trial of UB-312 in Parkinson's Disease

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**Objective:** Investigate whether target engagement can be demonstrated in CSF samples of Parkinson's disease (PD) patients immunized with UB-312, using an alpha-synuclein seed amplification assay (aSyn-SAA).

**Background:** UB-312 is an investigational active immunotherapy targeting pathological forms of alpha-synuclein (aSyn) for the treatment and prevention of synucleinopathies. In a Phase 1 study, UB-312 was generally safe, well tolerated, and immunogenic in both healthy volunteers and PD patients.

**Design/Methods:** 20 PD patients with unknown aSyn-SAA status were enrolled and randomly assigned to placebo or UB-312. Treatment was delivered IM on weeks 1, 5 and 13, and patients were followed until week 45. CSF samples were collected at baseline, week 21 and week 45. They were analyzed in the aSyn-SAA over 24 hours. The kinetics of aSyn amplification, including maximum fluorescence (Fmax), were analyzed.

**Results:** 19 out of the 20 patients met the criteria for positivity for aSyn seeds at baseline and week 21. Mean Fmax assessed longitudinally indicated a significant change from baseline ( $p < 0.01$ ), with placebo showing a 2.8% increase, 300/100/100ug showing a 19.8% decrease and 300/300/300ug showing a 15.2 % decrease at week 45. Unplanned analyses confirmed a significant decrease in Fmax by week 45 in patients with detectable UB-312 antibodies in CSF as compared to patients with no detectable CSF antibodies ( $p < 0.01$ ).

**Conclusions:** Our data indicate that target engagement was achieved in the CSF of several treated PD patients. These encouraging data support further development of UB-312. Dosing optimization and trial in a larger patient population will be conducted to confirm these results.





## **VISIONARY-MS Long-Term Extension: A Multi-Centre, Open-Label Long-Term Extension Study of CNM-Au8 in Patients with Stable Relapsing Multiple Sclerosis**

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**Objective:** VISIONARY-MS LTE trial assessed the long-term safety, efficacy, tolerability, and pharmacokinetics of CNM-Au8 30mg on participants with stable relapsing MS (RMS) over 96 weeks following completion of the 48-week double-blind period.

**Background:** CNM-Au8 is a neuroprotective investigational drug that catalytically enhances cellular metabolic energy. Results from the double-blind period demonstrated that CNM-Au8 treatment improved low contrast letter acuity (LCLA, 1<sup>o</sup> endpoint) and global neurological function assessed by the modified MS Functional Composite (2<sup>o</sup> endpoint) compared to placebo in stable RMS patients receiving approved disease-modifying immunomodulatory therapy (DMTs) as standard of care. Here we present analyses from the long-term open-label extension (LTE) study of participants from VISIONARY-MS LTE.

**Design/Methods:** The VISIONARY-LTE participants received daily doses of CNM-Au8 30mg. In addition to safety, functional endpoints were assessed at clinical visits every 12 weeks: LCLA for each eye by 2.5% Sloan letter chart, modified MSFC score that including the Timed 25-Foot Walk (T25FWT), Symbol Digit Modality Test (SDMT), 9-Hole Peg Test (9HPT, dominant and non-dominant hands), and LCLA (both eyes).

**Results:** 55 of 69 eligible participants (80%) originally randomized were eligible and participated in the LTE. The LS-mean difference (SE) at week 144 for: (i) LCLA change across both eyes vs. the original randomization baseline of participants assigned to CNM-Au8 was +8.7 letters (1.88), 95% CI: 5.0-12.4,  $p < 0.0001$  (ii) SDMT change vs. the original randomization baseline of participants assigned to CNM-Au8 was +8.03 (1.52), 95% CI: 5.01-11.0,  $p < 0.0001$ . Improvements during the double-blind period were maintained in the LTE for T25FWT and 9HPT. Individual treatment responses showed consistent improvement with substantial gains in low contrast vision and cognition. Observed LCLA change from the end of the double-blind period ranged up to 38 letters across both eyes.

**Conclusions:** These results provide long-term evidence for sustained improvements in neurological functions in stable RMS patients treated with CNM-Au8 adjunctively to DMTs.



## **Lecanemab for the Treatment of Early Alzheimer's Disease: The Extension of Efficacy Results from Clarity AD**

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**Objective:** To report the initial findings from the ongoing lecanemab Clarity AD open-label extension (OLE) study, in which we evaluated whether the treatment benefits were maintained up to 30 months in participants with early Alzheimer's disease (AD).

**Background:** Lecanemab is an anti-amyloid monoclonal antibody that binds with highest affinity to soluble A $\beta$  protofibrils, which are more toxic than monomers or insoluble fibrils/plaque. In the 18-month phase 3 Clarity AD study, lecanemab demonstrated a consistent slowing of decline in clinical (global, cognitive, functional, and quality of life) outcomes, and reduction in brain amyloid in early AD.

**Design/Methods:** Clarity AD is an 18-month, randomized study (core) in patients with early AD, with an OLE phase where eligible participants received open-label lecanemab. Clinical (CDR-SB, ADAS-Cog14, and ADCS-MCI-ADL) and biomarker (PET, A $\beta$ 42/40 ratio, and ptau181) outcomes were evaluated overall and by examining 'delayed start' (core:placebo followed by OLE:lecanemab) and 'early start' (core:lecanemab followed by OLE:lecanemab) cohorts. Analyses by core baseline tau PET levels were conducted from the tau PET sub-study.

**Results:** Overall, 1385 participants enrolled in the OLE. Across clinical endpoints, lecanemab-treated participants continued to benefit through 24 months. Separation between early and delayed start was maintained between 18 and 24 months ( $p < 0.05$ ), with a similar disease trajectory when all participants received lecanemab. Biomarker changes continued to improve and were seen in as early as 3 months in newly-treated lecanemab participants. Across assessments, consistent rates of clinical stability or improvements were observed regardless of baseline tau levels, with the highest rates of improvements observed for the low tau group at 24 months (no decline:79%; improvement:50%). Preliminary 30-month data will be presented.

**Conclusions:** Treatment differences with ongoing lecanemab treatment through 30 months, relative to the newly treated lecanemab participants, is consistent with a disease-modifying effect. Delayed start and lower pathology group results support early initiation of treatment with lecanemab.



## Long-term Efficacy of Endovascular Thrombectomy in Patients with Large Core Stroke from a Randomized Controlled Trial of Endovascular Thrombectomy for Large Ischemic Strokes (SELECT2)

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**Objective:** To evaluate EVT efficacy and safety in the SELECT-2 trial using clinical outcomes at 1-year follow-up.

**Background:** Multiple clinical trials recently established the efficacy and safety of endovascular thrombectomy in patients with large core strokes. However, all trials used functional status at 90-day follow-up as their primary outcomes and long-term efficacy of thrombectomy procedure in patients with large core strokes is not yet established.

**Design/Methods:** SELECT2 was a phase III international, multicenter, prospective, randomized, open-label trial with blinded endpoint assessment and randomized patients with a large ischemic core on noncontrast CT (ASPECTS 3-5), perfusion imaging (tissue volume with relative cerebral blood flow <30% of 50 ml or larger) or magnetic resonance imaging (tissue volume with apparent diffusion coefficient of 620 x 106 mm<sup>2</sup>/s of 50 ml or larger to receive EVT + best medical management or best medical management only. Primary outcome was modified Rankin Scale (mRS) score at 1-year follow-up, evaluated using generalized odds ratio. Secondary outcomes included functional independence (mRS 0-2), independent ambulation (mRS 0-3) and quality of life scores at 1- year follow-up.

**Results:** 329/352 (93%) patients completed 1-year follow-up for primary outcome at 31 sites across US, Canada, Spain, Australia and New Zealand. Thrombectomy significantly improved the 1-year modified Rankin Scale score distribution(WMW probability of superiority=0.59, 95%CI: 0.53to0.64, p=0.0019; Generalised odds ratio=1.43,95%CI:1.14to1.78), functional independence(EVT: 24% vs MM: 6%, RR: 3.17,95%CI: 1.73to5.79) and independent ambulation(EVT: 37% vs MM: 18%, RR: 1.85,95%CI:1.30to2.63) versus medical care alone. Effect estimates favored EVT across ASPECTS (0-2: GenOR: 1.20, 95%CI:0.58-2.51, 3-5: GenOR: 1.47,95%CI:1.14to1.88, 6-10: GenOR:1.44,95% CI:0.80-2.61) and ischemic core (≥70ml: GenOR:1.33,95%CI:1.04to1.70, ≥100ml: GenOR:1.08,95% CI: 0.81to1.44, ≥100ml: GenOR: 1.44,95% CI: 0.90to2.31)strata.

**Conclusions:** Acute ischemic stroke patients with a large core infarct, who were randomized to thrombectomy demonstrated a significant functional outcome improvement at 1-year follow-up as compared to medical care, which persisted across ischemic core strata on imaging.



## **A Phase 1 Study, INTERCEPT-AD, of ACU193: Safety, Target Engagement, and Biomarker Changes**

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**Objective:** To investigate safety and biomarker effects of ACU193, a monoclonal antibody (mAb) selective for soluble amyloid  $\beta$  oligomers (A $\beta$ Os), in a phase 1 trial of participants with early AD.

**Background:** Soluble globular A $\beta$ Os may instigate AD neurodegeneration and have not previously been targeted by a mAb in the clinic. ACU193 is a humanized IgG2 subclass mAb targeting soluble A $\beta$ Os. Some of these data have been presented previously<sup>1,2</sup>.

**Design/Methods:** INTERCEPT-AD was a double-blind, placebo-controlled study incorporating four single dose cohorts with doses ranging from 2 mg/kg to 60 mg/kg and three multiple-dose cohorts receiving three doses of ACU193 (10 or 60 mg/kg every four weeks or 25 mg/kg every two weeks) or placebo (NCT04931459). Participants clinically had MCI or mild dementia and amyloid positivity was confirmed by florbetapir PET. Safety assessments included magnetic resonance imaging. CSF and plasma were used for target engagement and biomarker assessments.

**Results:** Sixty-two participants were randomized; mean ages of cohorts were 67.8 to 72.1 years. Of 48 participants treated with ACU193, 5 developed amyloid-related imaging abnormalities – edema (ARIA-E), one of whom had transient mild symptoms. CSF analyses showed robust target engagement (ACU193 bound to A $\beta$ Os) and apparent improvement in pTau181, neurogranin and VAMP2 with ACU193 treatment in multiple-dose cohorts. Plasma analyses showed apparent improvement in GFAP, pTau181, and pTau217 with ACU193 treatment in the 60 mg/kg multipledose cohort.

**Conclusions:** ACU193 was well-tolerated in participants with early AD with relatively low incidence of ARIA-E. CSF and plasma biomarkers showed target engagement and a consistent effect of ACU193 on AD biomarkers. Clinical efficacy and biomarker changes will be evaluated in a planned phase 2/3 study.  
1. Siemers ER, Feaster T, Skljarevski V et al. *Alzheimer's Dement*. 2023;19(Suppl.24) :e082821. <https://doi.org/10.1002/alz.082821> 2. Trame M, Dodds M, Cline E et al. *J Prev Alz Dis* 2023;10(S1):S4-S55. <http://dx.doi.org/10.14283/jpad.2022.129>



### **Results From a Global Phase 3 Trial Evaluating an Oral, Fixed-Dose Combination of Sodium Phenylbutyrate and Taurursodiol in Amyotrophic Lateral Sclerosis (PHOENIX)**

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**Objective:** The global phase 3, randomized, placebo-controlled PHOENIX trial evaluated the safety and efficacy of an oral, fixed-dose combination of sodium phenylbutyrate and taurursodiol (PB&TURSO) in amyotrophic lateral sclerosis (ALS).

**Background:** In the phase 2 CENTAUR trial, PB&TURSO significantly slowed functional decline and prolonged survival duration compared with placebo in adults with definite ALS (revised El Escorial criteria), symptom onset  $\leq 18$  months, and baseline slow vital capacity (SVC)  $>60\%$ . PHOENIX was designed to evaluate PB&TURSO in a larger population of people living with ALS over a longer placebo-controlled duration than in CENTAUR (48 weeks vs 24 weeks, respectively).

**Design/Methods:** Adults with clinically definite or clinically probable ALS, symptom onset  $<24$  months, and SVC  $\geq 55\%$  were enrolled from 69 European and US sites and randomized 3:2 to receive PB&TURSO or placebo for 48 weeks. The primary end point was change from baseline to Week 48 in ALS Functional Rating Scale–Revised (ALSFRS-R) total score, evaluated using the mortality adjusted mixed-effects model, known as Mortality Adjusted Progression (MAP). Secondary end points included change from baseline to Week 48 in the 40-item ALS Assessment Questionnaire and in SVC, change from baseline to Week 24 in ALSFRS-R total score, and overall survival (to be assessed over longer-term follow-up at the final data analysis). Safety assessments included adverse event incidence and severity.

**Results:** Six hundred sixty-four participants (Europe,  $n=552$ ; US,  $n=112$ ) with a mean (SD) age of 59.5 (10.81) years were enrolled. Most identified as male (62%) and White (83%); 22% had bulbar-onset disease. Mean (SD) time since ALS symptom onset was 14.4 (5.30) months. At screening, 92% and 3% of participants were receiving stable-dose riluzole and edaravone, respectively.

**Conclusions:** Topline results including primary efficacy and safety data will be presented at the Annual Meeting of the American Academy of Neurology pending data availability.





## **Clinical Activity and Safety of GTX-102, an Investigational Antisense Oligonucleotide for the Treatment of Patients With Angelman Syndrome**

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**Objective:** Describe the clinical activity of GTX-102, an investigational intrathecally administered antisense oligonucleotide (ASO) designed to target the UBE3A antisense transcript in patients with Angelman syndrome (AS).

**Background:** AS, a rare neurodevelopmental disorder with no approved disease modifying treatment, is characterized by seizures, severe speech and cognitive impairment, sleep disorders, and motor dysfunction.

**Design/Methods:** GTX-102-001 is an ongoing phase 1/2 open-label study with dose-escalation and dose-expansion cohorts (ClinicalTrials.gov Identifier: NCT04259281). Eligible patients with genetic confirmation of full maternal UBE3A gene deletion receive 3 to 4 monthly loading GTX-102 injections followed by maintenance dosing every 3 months. Data from dose-escalation cohorts 4 to 7 through maintenance dose 4 (Study Day 422) are outlined below. Dose-expansion cohorts received similar doses to cohorts 4 to 7.

**Results:** As of the data cutoff for this analysis, 15 participants were enrolled across cohorts 4 to 7. A Multi-Domain Responder Index (MDRI) captured broad clinical benefit ( $p=0.001$ ) across five domains, including sleep and behavior (Angelman Severity Assessment), Receptive Communication, Cognition, and Gross Motor function (Bayley-4). Bayley-4 mean (SD) change from Baseline to Study Day 422 was 11.1 (6.5) for the Receptive Communication Growth Scale Value (GSV), 12.6 (9.7) for the Cognition GSV, and 5.1 (2.8) for the Gross Motor GSV, all exceeding natural history comparator values. Following the loading phase, GTX-102 was associated with increased sleep spindle rate and duration, and reductions in relative delta power by electroencephalogram (EEG). Across all participants in the dose-escalation and dose-expansion cohorts ( $n=69$ ), there were no unexpected adverse events or ASO class effects.

**Conclusions:** Across the dose-escalation cohorts, participants had significant improvements in Bayley-4 Receptive Communication, Cognition, and Gross Motor domains and quantitative improvement in EEG relative delta power and sleep. Additional results from the dose-expansion cohorts up to maintenance dose 2 (Study Day 254) will be reported.



## **Positive Disease Modifying Effects of Oral ALZ-801 on Plasma Biomarkers, Volumetric MRI and Cognition at 104 Weeks: Results of a Phase 2 Study in APOE4 Carriers with Early Alzheimer's Disease**

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**Objective:** To evaluate ALZ-801's effects on plasma and imaging biomarkers of Alzheimer's disease (AD).

**Background:** ALZ-801 (valiltramiprosate), an oral brain-penetrant amyloid-oligomer inhibitor is completing a Phase 3 78-week trial in APOE4/4 homozygotes Early AD (EAD) subjects. The Phase 2 study evaluated its effects (265mg BID) on plasma biomarkers, MRI and cognition in EAD APOE4 carriers over 2 years. Plasma p-tau181 is elevated in AD and reduced by efficacious doses of lecanemab and aducanumab.

**Design/Methods:** This 104-week, open-label study enrolled 84 subjects (MMSE 22-30, CDR-G 0.5-1, positive amyloid-PET or CSF biomarkers). Plasma and clinical testing were every 13 weeks, MRI every 52 weeks. Primary outcome was plasma p-tau181, cognitive tests were Rey Auditory-Verbal-Learning-Test (RAVLT) and Digit-Symbol-Substitution-Test (DSST). Dr. Blennow's Laboratory (Sweden) conducted plasma biomarker analyses (Simoa, EuroImmun assays). Observed data changes-from-baseline were analyzed with 2-sided simple t-tests.

**Results:** 84 subjects were enrolled (51% female, age 69 years, MMSE 26.0, 70%/30% had MCI/Mild AD; 70 completed 104-weeks. Plasma p-tau181 showed significant reductions at all timepoints reaching 31%-43% over 52-104 weeks ( $p=0.045$ ), A $\beta$ 42 decreased ~4% over 104 weeks ( $p=0.042$ ). Hippocampus atrophy (3.6%) was ~28% less than matched external control (ADNI-1 study). RAVLT-total memory and DSST improved at 26 weeks, remaining above/at baseline at 104 weeks; 50% and 33% of MCI and Mild AD subjects maintained their CDR-G stage. Cognitive stabilization correlated with decreased hippocampal atrophy (Spearman's  $r=0.38-0.43$ ,  $p\leq 0.002$ ); and cortical thinning ( $r=0.35-0.58$ ,  $p\leq 0.004$ ). COVID-19 infection, nausea, decreased appetite were the main AEs, with no ARIA-E.

**Conclusions:** Over 2 years, oral ALZ-801 reduced plasma p-tau181 and A $\beta$ 42 significantly suggesting improved amyloid clearance. Cognitive stabilization correlated strongly with reduced brain atrophy, both showing treatment benefit compared to external control. No ARIA-E/vasogenic edema was detected. These biomarker results support the disease-modifying effects of ALZ-801 in Early AD with promising clinical efficacy and favorable safety in APOE4 carriers.