Efficacy and safety of trofinetide for the treatment of Rett syndrome: results from the pivotal phase 3 LAVENDER study

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Objective:
To investigate efficacy and safety of trofinetide in girls and young women with Rett syndrome (RTT).

Background:
RTT is a debilitating genetic neurodevelopmental disorder that primarily affects females and lacks an approved treatment. Trofinetide is a synthetic analog of glycine–proline–glutamate, a naturally occurring tripeptide cleaved from insulin-like growth factor 1. Phase 2 studies in RTT demonstrated a clinical benefit over placebo in clinician- and caregiver-assessed efficacy measures.

Design/Methods:
Females with RTT, aged 5–20 years, were randomized 1:1 to twice-daily oral trofinetide or placebo for 12 weeks. Efficacy endpoints included the Rett Syndrome Behaviour Questionnaire (RSBQ), a caregiver assessment of core RTT symptoms (co-primary), the Clinical Global Impression–Improvement (CGI-I) scale (co-primary), and the Communication and Symbolic Behavior Scales Developmental Profile™ Infant-Toddler Checklist-Social (CSBS-DP-IT Social) composite score (key secondary). Safety measures included adverse events.

Results:
Overall, 187 individuals were randomized to trofinetide (n=93) or placebo (n=94). After 12 weeks of treatment, trofinetide demonstrated a statistically significant improvement over placebo for co-primary and key secondary endpoints. Least squares (LS) mean change from baseline to week 12 in the RSBQ for trofinetide vs. placebo was -4.9 vs. -1.7 (p=0.0175; Cohen's d effect size = 0.37), LS mean CGI-I score at week 12 was 3.5 vs. 3.8 (p=0.0030; Cohens' d effect size = 0.47), and LS mean change from baseline to week 12 in the CSBS-DP-IT Social composite score was -0.1 vs. -1.1 (p=0.0064; Cohen's d effect size = 0.43). Serious adverse events were reported in 3.2% of participants in the trofinetide and placebo groups. The most common adverse event in the trofinetide and placebo groups was diarrhea (80.6% and 19.1%, respectively) with 98% of all cases experiencing mild-to-moderate severity.

Conclusions:
This study demonstrated that trofinetide is efficacious and has an acceptable safety profile in girls and women with RTT.

The pivotal multi-center, randomized, double-blind, placebo-controlled trial of Intra-Erythrocyte Dexamethasone Sodium Phosphate (ATTeST) on the neurological motor function of people with Ataxia Telangiectasia

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Objective:

The phase 3 ATTeST study assessed the efficacy and safety of monthly infusions of intra-erythrocyte dexamethasone phosphate (EDS) in patients with A-T.

Background:
A-T is a devastating recessive disorder characterized by progressive neurological deterioration, immunodeficiency and/or malignancy.

Design/Methods:

175 A-T patients (mean age 10.1 ± 4.17 years) were randomized to EDS dose ranges of ~5-10 mg, or ~14-22 mg, or placebo every 30 days. The primary efficacy outcome was the modified international cooperative ataxia rating scale (mICARS and RmICARS). The trial was registered with ClinicalTrials.gov number: NCT02770807 and is completed, the study sponsor is EryDel, SpA.

Results:

Between March 2017 and March 2020, 175 patients were enrolled and 164 were randomized; 132 (80.5 %) completed the 24 weeks of the primary efficacy period. The Full Analysis Set (FAS, N=164) showed favourable primary outcomes in the treated groups compared to placebo, but did not reach statistical significance.

The per-protocol (PP) analysis (N=107) showed slower rate of neurologic deterioration for both doses compared to placebo (mICARS p=0.004 low dose and 0.019 high dose; RmICARS p=0.003 and 0.036 high dose). The *a priori* age 6–9-year olds' ITT analysis (N=89) showed a statistically significant favourable outcome for high dose *vs* placebo (mICARS p=0.019 and RmICARS p=0.028).Treatment-emergent adverse events occurred in 43 (73%) 47 (82%),and 43 (73%) patients in the low dose, high dose, and placebo group, respectively, and serious adverse events in 6 (10%), 7 (12%), and 7 (12%) patients respectively. There were no clinically important known adverse effects of corticosteroids and no deaths.

Conclusions:

The 6 months safety analysis showed that EDS was well tolerated and did not identify any alarming safety signals that might be expected with chronic steroid use. The efficacy analysis showed that progression of neurological motor decline was significantly blocked by the high dose EDS treatment, more clearly evident in the younger children.

Ecopipam in Children and Adolescents with Tourette Syndrome: Results from a Randomized, Double-Blind, Placebo-Controlled Phase 2b Study

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Objective:
Evaluate the efficacy and safety of ecopipam in children and adolescents with Tourette syndrome (TS).

Background:
Ecopipam, a first-in-class selective dopamine-1 (D1) receptor antagonist, is in clinical development for pediatric patients with TS. In prior Phase 2 studies in TS, ecopipam reduced tics in children and adults and demonstrated a history of low metabolic and movement-related adverse events.

Design/Methods:
Patients with TS were randomized 1:1 to ecopipam or placebo for a 4-week titration, an 8-week maintenance, and a 1-week tapering period. The primary endpoint was mean change from Baseline (BL) to Week 12 for the Yale Global Tic Severity Score - Total Tic Score (YGTSS-TTS). Clinical Global Impression of Tourette Syndrome Severity (CGI-TS-S) was the key secondary endpoint. Safety and tolerability were evaluated at each study visit.

Results:
153 patients were randomized and 149 included in the modified intent-to-treat population (74 ecopipam, 75 placebo). A significant improvement (LS mean [SE] difference: -3.44 [1.35], 95% CI: -6.09, -0.79, p=0.011) in the YGTSS-TTS from BL to Week 12 was observed for ecopipam vs. placebo (30% reduction from BL to Week 12, effect size = 0.48). Similar results were observed among those ages 6 to 11 years (LS mean [SE] difference: -4.95 [2.50], 95% CI: -9.99, 0.10, p=0.054) and those ages 12 to 17 years (LS mean [SE] difference: -3.37 [1.58], 95% CI: -6.51, -0.24, p=0.035). Mean change from BL to Week 12 was significant for CGI-TS-S (p=0.001). Treatment-related AEs occurred in 26 (34%) patients with ecopipam and 16 (21%) with placebo, most commonly headache (9.2%), fatigue (6.6%), somnolence (6.6%), and restlessness (5.3%). No metabolic or movement-related AEs or treatment-related serious AEs occurred.

Conclusions:
Among children and adolescents with TS, ecopipam significantly reduced motor and phonic tics with similar results between age groups and was safe and well-tolerated.

Efficacy and safety of P2B001 in the management of early Parkinson's disease. Results from a phase 3, randomized, double-blind, double-dummy controlled trial

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Objective:
Evaluate the efficacy and safety of P2B001 compared with its components and with generic Extended-Release pramipexole (ER-PPX, calibration arm) in early Parkinson's disease (PD).

Background:
P2B001 is novel, fixed-dose, once-daily combination of ER formulations of pramipexole and rasagiline (0.6/0.75mg), both components at low doses that are not individually available on the market.

Design/Methods:
Untreated patients (35-80 years, disease duration <3 years) were randomized double-blind (2:2:2:1) to 12-weeks treatment with P2B001, pramipexole-ER (PPX) 0.6mg, rasagiline-ER (RAS) 0.75mg, or marketed ER-PPX (titrated). The primary efficacy endpoint compared the change from baseline to Week 12 in UPDRS-Total score (Parts II+III) for P2B001 with its individual components. The first secondary endpoint compared the change from baseline in Epworth Sleepiness Scale (ESS) for P2B001 versus ER-PPX.

Results:
519 patients were randomized and treated (P2B001 =150, PPX 0.6mg =148, RAS 0.75mg =147, ER-PPX =74) and 90-93% per group completed 12-weeks treatment. P2B001 provided significantly superior symptomatic efficacy to its components; mean ±SE change in UPDRS-Total scores were -7.98 ±0.60 for P2B001 compared to -5.32 ±0.61 for PPX 0.6mg (treatment difference [TD]: -2.66 [-4.33, -1.00]; p=0.0018) and 4.69 ±0.61 for RAS 0.75mg (TD: -3.30 [-4.96, -1.63]; p=0.0001). P2B001 showed comparable efficacy to ER-PPX (TD: 0.37 [-1.67, 2.42]; p=0.71) with significantly less daytime sleepiness (mean ±SE changes from baseline in ESS-Total scores were -0.33 ±0.25 for P2B001 vs. 2.33 ±0.36 for ER-PPX (TD: -2.66 [-3.50, -1.81]; p<0.0001)). Fewer dopaminergic adverse events were reported with P2B001 vs ER-PPX (44.7% vs 66.2%), including somnolence (14.7% vs. 31.1%) and orthostatic hypotension (2.7% vs. 12.2%).

Conclusions:
The study met its primary and secondary endpoint and treatment was well-tolerated with fewer dopaminergic AEs than ER-PPX. These findings support the potential of P2B001 as a first-line, once-daily treatment for people with early PD that offers effective symptomatic control with a favorable safety profile and no need for titration.

Plasma-Based Biomarkers in Phase 2 Study of Donanemab in Early, Symptomatic Alzheimer's Disease

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Objective:
Explore the effect of donanemab on plasma biomarker levels associated with Alzheimer's disease (AD) and their association with amyloid and tau imaging measurements.

Background:
TRAILBLAZER-ALZ (NCT03367403) was a randomized, double-blind, placebo-controlled, phase 2 study of donanemab (antibody targeting mature amyloid plaques) in early, symptomatic AD. In this trial, donanemab demonstrated robust amyloid plaque reduction and slowing of tau accumulation as measured using positron emission tomography (PET).

Design/Methods:
Plasma samples were collected regularly from baseline through week 76. Plasma biomarkers, including Aβ 42/40, glial fibrillary acidic protein (GFAP), neurofilament light chain (NfL) and phosphorylated (P)-tau217, were measured using Quanterix Simoa HD-X technology. All plasma values were log10-transformed in pre-specified analyses. Spearman's rank analyses were performed for correlation coefficients.

Results:
At baseline, plasma P-tau217 levels were statistically significantly correlated with amyloid plaque level (R=0.148, p=0.0243) and global tau deposition (R=0.361, p<0.0001) on PET. Plasma levels of P-tau217 and GFAP were significantly reduced after 12 weeks of donanemab treatment versus placebo. This reduction was sustained over the 76 weeks of study. No significant differences in plasma levels of Aβ 42/40 and NfL were observed between treatment arms at 76 weeks. The changes in plasma P-tau217 and GFAP levels were positively correlated with percent change in amyloid plaque level on PET (R=0.484, p<0.0001 and R=0.453, p<0.0001, respectively). A significant positive correlation was observed between the change in plasma P-tau217 and change in tau deposition on PET in the frontal (R=0.243, p=0.0019) and temporal (R=0.177, p=0.0247) lobes at 76 weeks and trended towards significance in the parietal lobe (R=0.154, p=0.0516). Additionally, plasma P-tau217 and GFAP levels were significantly correlated at baseline and for 76-week change.

Conclusions:

P-tau217 and GFAP plasma levels significantly lowered with donanemab treatment, suggesting that plasma biomarkers may be useful as pharmacodynamic measures of downstream treatment effects of amyloid plaque reduction in early AD.

Long-Term Safety of a Fully Implanted Endovascular Brain-Computer Interface for Severe Paralysis: Results of SWITCH, a First-in-Human Study

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Objective:
To assess safety of an endovascular motor neuroprosthesis (MNP) and feasibility of using the implant to control a computer by thought.

Background:
The MNP provides direct communication between the brain and an external device by recording and decoding signals from the precentral gyrus as the result of movement intention. To date, implantation of MNPs has required surgery involving removal of a portion of the skull and placement of electrodes on the brain. A recently developed minimally invasive MNP reaches the brain by vascular access, without need for a craniotomy.

Design/Methods:
Subjects with paralysis were implanted with the endovascular device (Stentrode, Synchron, Brooklyn, NY) using a catheter to guide placement in the superior sagittal sinus. The device was attached to an electronics unit in a subcutaneous pocket to relay brain signals from the motor cortex into commands for a laptop computer. Safety endpoints were device-related serious adverse events resulting in death or increased disability during the 12-month post-implant evaluation period, and target vessel patency and incidence of device migration at 3 and 12 months. The study also recorded signal fidelity and stability over 12 months and use of the brain-computer interface to perform routine digital tasks.

Results:
The study enrolled five subjects with amyotrophic lateral sclerosis; four had suitable anatomy and underwent the implant procedure. All four subjects successfully completed the 12-month follow-up with no serious adverse events. Post-operative imaging demonstrated patent blood vessels in all subjects and no device migration. All subjects learned to use the MNP with eye tracking for routine computer use. The decoder developed during the study allowed the final participant to control a computer independently without an eye tracker.

Conclusions:
In a first-in-human study, four subjects were implanted with an endovascular brain-computer interface. The study met its safety endpoints, allowing subjects with paralysis to operate a computer for daily tasks.

SAGE-718 in Patients With Mild Cognitive Impairment or Mild Dementia due to Alzheimer's Disease: Results From the Phase 2 LUMINARY Study

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Objective:
To evaluate the safety/tolerability of SAGE-718 and its effects on cognitive symptoms in patients with Alzheimer's disease (AD).

Background:
Cognitive impairment has a deleterious impact on patients with AD and their caregivers; new therapies are needed. SAGE-718, a novel N-methyl-D-aspartate receptor positive allosteric modulator, is being investigated for the treatment of cognitive impairment in patients with neurodegenerative diseases such as AD.

Design/Methods:
LUMINARY (NCT04602624) is an open-label, Phase 2 study evaluating SAGE-718 (3mg QD for 14 days) in patients with AD. Patients (aged 50–80 years) with Montreal Cognitive Assessment (MoCA) scores of 15-24 were included. Treatment-emergent adverse event (TEAE) incidence through Day 28 (primary endpoint), other safety outcomes (secondary endpoints), and cognitive and functional assessments were analyzed.

Results:
Twenty-six patients (69.2% female; mean age 67 years), with a mean±SD MoCA of 20.7±2.61 were enrolled. Most patients (23/26) had a global Clinical Dementia Rating score of 0.5. Eight TEAEs were reported in 7 (26.9%) patients; all were mild/moderate; 6 were treatment related. No serious adverse events or deaths were reported. At Day 14, improvements from baseline were observed on multiple tests of executive functioning (Digit Symbol Substitution, Multitasking, One Touch Stockings, Spatial Working Memory, and 2-Back tests) and learning and memory (Pattern Recognition Memory and Verbal Recognition Memory tests). Statistically significant MoCA improvement (+2.3 points vs baseline) was observed at Day 28. No changes in attention/psychomotor speed were observed. Functional assessments also captured notable improvement in some patients (Clinical Global Impressions Scales and Amsterdam Instrumental Activities of Daily Living Questionnaire), particularly on items measuring aspects of complex/higher order activities.

Conclusions:
In this study, SAGE-718 was generally well tolerated and associated with cognitive and functional improvements in patients with AD. These results support further investigation of SAGE-718 for the treatment of cognitive impairment associated with AD and other neurodegenerative diseases.

Long-Term Survival of Randomized Participants Enrolled in the Phase 2 RESCUE-ALS Trial of CNM-Au8, A Cellular Energetic Catalyst

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Objective:

To investigate the efficacy and safety the novel cellular energetic catalyst, CNM-Au8, as a disease-modifying treatment for amyotrophic lateral sclerosis (ALS).

Background:

CNM-Au8, an oral suspension of clean-surfaced catalytically-active gold nanocrystals, enhances the energetic capacity of motor neurons via improved cellular energy metabolism resulting in significant neuroprotection and neurorepair in preclinical models. RESCUE-ALS was a phase 2, randomized, double-blind placebo-controlled clinical trial in early ALS. Treatment continuation was offered through an open-label extension (OLE). Long-term survival of all participants through 31-Dec-2021 (up to ~100 weeks from randomization) was evaluated.

Design/Methods:

ALS participants were randomized 1:1 to receive 30mg CNM-Au8 or placebo daily during the double-blind comparative period (36-weeks) followed by OLE treatment with CNM-Au8 (30mg/day). 45 participants were enrolled (n=23 active (CNM-Au8), n=22 matched placebo). Kaplan Meier survival analyses were conducted from randomization. Vital status and date of expiry was determined for all subjects, including those who withdrew or discontinued. Lost-to-follow-up (n=2) were censored at last contact. Sensitivity analyses compared observed survival versus predicted median survival derived from the published ENCALS model.

Results:

CNM-Au8 treatment demonstrated improved long-term survival versus placebo (deaths from randomization through 31-Dec-2021; CNM-Au8, n=3; placebo, n=8; HR: 0.342, 95% CI: 0.11, 1.12; p=0.096). Sensitivity analyses showed fewer CNM-Au8 deaths compared to ENCALS prediction (3 vs. 10 events; HR: 0.297, 95% CI: 0.10, 0.89; p=0.05). Furthermore, the subset of placebo participants who transitioned to CNM-Au8 in the OLE (n=16) also demonstrated improved survival versus ENCALS predicted (2 vs. 7 events; HR: 0.21, 95% CI: 0.056, 0.78; p=0.03).

Conclusions:

These results demonstrate improved long-term survival in participants originally randomized to CNM-Au8 treatment. Increased risk of death was observed in participants who (i) were originally randomized to placebo, or (ii) who did not transition into the OLE. These results support CNM-Au8 treatment as effective for ALS disease modification.

Comparative Safety and Efficacy of Different Corticosteroid Regimens for Duchenne Muscular Dystrophy: Results of an International Randomized Controlled Trial

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Objective:
This study compares efficacy and side effects of the three most commonly prescribed corticosteroid regimens in young boys with Duchenne muscular dystrophy (DMD).

Background:
Corticosteroids improve muscle function in boys with DMD and should be considered for all newly diagnosed patients, according to care recommendations. However, uncertainty regarding regimen and side effects has led to great variability in corticosteroid use. Corticosteroids are likely to be used in DMD for the foreseeable future.

Design/Methods:
In a randomized, double-blind, parallel-group clinical trial involving 32 sites in 5 countries, 196 corticosteroid-naïve boys age 4-7 years were randomized 1:1:1 to receive daily prednisone (0.75 mg/kg/day), daily deflazacort (0.9 mg/kg/day), or intermittent prednisone (0.75 mg/kg 10-days on/10-days off). Boys were assessed for three years. The three-dimensional primary outcome comprised rise from the floor velocity, forced vital capacity, and participant/parent global satisfaction with treatment. Secondary efficacy outcomes included 10-meter walk/run velocity, 6-minute walking distance and North Star Ambulatory Assessment total score. Safety outcomes included height and weight, behavioral measures, and frequency and severity of adverse events.

Results:
Daily prednisone and deflazacort were superior to intermittent, 10-days on/10- days off, prednisone for the primary outcome and all secondary motor function outcomes. There were no significant differences in efficacy between daily prednisone and deflazacort. There was greater weight gain with both daily and intermittent prednisone regimens than with deflazacort. Slowing of growth was less severe with the intermittent regimen than with the daily regimens, with daily deflazacort associated with the greatest slowing of growth.

Conclusions:
Daily steroid regimens demonstrated significantly greater efficacy in motor function than the intermittent, 10 days on 10 days off, prednisone regimen. The data support the standardization of corticosteroid prescription at the time of treatment initiation and could facilitate the interpretation of efficacy outcomes of clinical trials targeting young boys with DMD.

Cognitive Symptoms After Mild SARS-CoV-2 Infection Associate with Higher Levels of CSF Immune Activation and Immunovascular Markers

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Objective:
To measure cerebrospinal fluid (CSF) immune activation and immunovascular markers in individuals with cognitive post-acute sequelae of SARS-CoV-2 infection (PASC) who had mild COVID-19.

Background:
Cognitive PASC is a condition without identified biological correlates, although we reported a high rate of CSF abnormalities on clinically-available tests (77%). Theorized mechanisms include immune dysfunction.

Design/Methods:

We enrolled participants in recovery from documented SARS-CoV-2 infection not requiring hospitalization who endorsed new, persistent cognitive symptoms (cognitive PASC, n=23) or no cognitive symptoms (controls, n=10) on structured neurocognitive interview. Participants underwent neurological examination and neuropsychological testing. Optional lumbar puncture and CSF analysis of immune activation and immunovascular markers were performed in 54% (n=13 cognitive PASC, n=5 controls).

Results:
CSF was collected a median of 10.2 months after first COVID symptom without group differences in timing or demographics. Cognitive PASC participants had higher median levels of CSF acute phase reactants C-reactive protein (0.007 vs. 0.000 mg/L, p=0.004) and serum amyloid A (0.001 vs 0.000 mg/L, p=0.001) compared to controls, with trends in higher CSF immune activation markers interferon-gamma-inducible protein (IP-10; p=0.059), interleukin (IL)-8 (p=0.059), and immunovascular markers vascular endothelial growth factor-C (VEGF-C, p=0.095) and VEGFR-1 (the soluble receptor for VEGFs, p=0.059). Analyzing by time of cognitive symptom onset, acute onset cognitive PASC (n=7) associated with higher levels of CSF VEGF-C compared to delayed onset cognitive PASC (1+ months after first COVID symptom; n=5; 173 vs. 99 pg/mL p=0.048) and controls (79 pg/mL, p=0.048). Acute onset cognitive PASC had higher CSF levels of IP-10 (p=0.030), IL-8 (p=0.048), placental growth factor (p=0.030), and intercellular adhesion molecule-1 (p=0.045) compared to controls.

Conclusions:
We found higher levels of CSF immune activation and immunovascular markers in cognitive PASC cases compared to controls; some markers showed specificity for acute onset cognitive PASC. These findings imply intrathecal immune activation and endothelial activation/dysfunction may contribute to cognitive PASC.

Lecanemab: An Assessment of the Clinical Effects, the Correlation of Plasma Aβ 42/40 Ratio With Changes in Brain Amyloid PET SUVr, and Safety from the Core and Open Label Extension of the Phase 2 Proof-of-Concept Study, BAN2401-G000-201, in Subjects With Early Alzheimer's Disease (AD)

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Objective:
To provide updated efficacy and safety results from the lecanemab phase 2 study, including data on the longitudinal plasma Aβ 42/40 ratio (C2N PrecivityAD assay) and the relationship to longitudinal amyloid PET in the core, gap period, and OLE.

Background:
Lecanemab (BAN2401), a humanized IgG1 monoclonal antibody, preferentially binds large soluble aggregated Aβ species and has demonstrated robust brain fibrillar amyloid reduction correlating with slowing clinical decline in early AD (Swanson et al. Alz Res Therapy 13; 2021).

Design/Methods:
The lecanemab Study 201 Core was a randomized placebo controlled study in which 856 patients were randomized to five dose regimens or placebo. An open-label extension (OLE) of Study 201, was initiated to allow patients to receive open-label lecanemab 10mg/kg-biweekly for up to 24 months, with an intervening off-treatment period (gap period) ranging from 9-59 months (mean 24 months).

Results:
Treatment differences vs placebo at 18 months in the core were maintained across 3 clinical assessments at OLE baseline. The rates of progression during the gap were similar in lecanemab and placebo patients. In the OLE, progression on all clinical endpoints plateaued with lecanemab for patient with OLE baseline global CDR 0.5 or 1, while those with global CDR >1 continued to progress, though less than a comparative natural disease progression rate (ADNI). Lecanemab produced dose-dependent reductions in PET SUVr, with corresponding increases in plasma Aβ 42/40 ratio in core and OLE. Consistent with core safety findings, lecanemab was well-tolerated with <10% incidence of ARIA-E at 10-mg/kg biweekly in the OLE.

Conclusions:
Findings from the lecanemab study 201 suggest that continued treatment may be beneficial for subjects with early AD. These data are hypothesis generating and will be further explored in ongoing phase 3 lecanemab clinical trials in early AD and preclinical AD (Clarity AD and AHEAD 3-45, respectively).

Effectiveness of COVID-19 Vaccines in Multiple Sclerosis Patients Receiving Disease-Modifying Therapies in England

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Objective:
To assess the clinical effectiveness of COVID-19 vaccines in multiple sclerosis (MS) patients receiving disease-modifying therapies (DMTs)

Background:
Immunological studies have measured humoral and cellular immune responses to COVID-19 vaccines among MS patients receiving DMTs, but their clinical relevance is unclear. Using cumulative data of the entire population of MS patients on DMTs in England, we showed that the incidence of SARS-CoV-2 infection among patients on fingolimod and ocrelizumab did not decrease following mass vaccination as opposed to the general population or patients on other MS DMTs.

Design/Methods:
We have now access to individual-level data on COVID-19 vaccination and COVID-19 related outcomes of all MS patients receiving DMTs in England from the start of the pandemic. These prospectively and longitudinally collected data are provided by the National Health Service (NHS) England and NHS Improvement and the UK Health Security Agency. We calculated the incidence of SARS-CoV-2 infection (i.e., a positive test) and COVID-19 related hospitalisation (i.e., hospitalisation of >1 day within 0-28 days of a positive test) following vaccination (i.e., ≥14 days after the second dose) from December-2020 to January-2022.

Results:
A total of 38,039 MS patients on DMTs (90%) had at least two doses of COVID-19 vaccines. Following vaccination, the incidence of infection was 24% (859/3624) for ocrelizumab, 22% (819/3797) for fingolimod, and ranged from 11% to 16% for other DMTs. The hospitalisation rate among infected patients was 7% (n=61) for ocrelizumab, 4% (n=33) for fingolimod, and ranged from 1% to 4% for other DMTs.

Conclusions:
Patients on ocrelizumab have higher rates of infection and hospitalisation than other DMTs using current vaccination protocols. Patients on fingolimod also have higher rates of infection but their hospitalisation rate is similar to other DMTs. Further analysis of booster vaccination, unvaccinated patients, and COVID-19 related mortality is ongoing and will be presented at the meeting.

KINECT HD: Results from a Randomized, Double-Blind, Placebo-Controlled Phase 3 Trial of Valbenazine for Chorea Associated with Huntington Disease (HD)

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Objective:
KINECT-HD evaluated the efficacy, safety, and tolerability of valbenazine for the treatment of chorea associated with Huntington Disease (HD).

Background:
Chorea is a hallmark motor symptom of HD impacting motor function. Valbenazine, a potent and selective vesicular monoamine transporter 2 inhibitor was approved for the treatment of tardive dyskinesia in the US (2017).

Design/Methods:
KINECT-HD, a Phase 3, randomized, double-blind, 12-week, placebo-controlled study in North America, enrolled 128 adults 18 to 75 years of age with chorea and genetically confirmed HD. Participants randomized 1:1 (placebo: valbenazine, once daily) were initiated with 40mg and titrated up to 80mg as tolerated. Primary outcome was change in chorea severity, using the Total Maximal Chorea (TMC) score of the Unified Huntington's Disease Rating Scale (UHDRS®) from baseline (average score at screening and baseline visit) to the maintenance period (average score at weeks 10 and 12). Safety assessments included adverse event (AE) rates, laboratory, ECG, and psychiatric assessments. Secondary outcome measures included clinician and patient-reported outcomes.

Results:

Average TMC score during the baseline period was 12.2 (SD 2.3). Valbenazine demonstrated a statistically significant improvement in chorea severity with a placebo-adjusted mean reduction of 3.2 units in TMC score vs. placebo (LS Mean change from baseline -4.6 vs. -1.4; P<0.0001). Statistically significant secondary endpoints of Clinical Global Impression of Change (CGI-C) Response Status and Patient Global Impression of Change (PGI-C) Response Status favored valbenazine treatment. Neuro-QOL upper and lower extremity physical function endpoints were not statistically significant. Most commonly reported AE was somnolence (valbenazine: 15.6%, placebo: 3.2%). No suicidal behavior or worsening of suicidal ideation was observed in the valbenazine treated subjects.

Conclusions:
Once-daily administration of valbenazine was associated with significant improvement in chorea. Valbenazine was well tolerated; treatment emergent adverse events observed in this trial were consistent with the known safety profile of valbenazine.