UB-313, an Investigational CGRP Vaccine for the Prevention of Migraine

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Objective:
Preclinical characterization of UB-313 in support of clinical development

Background:
Monoclonal antibodies against CGRP have demonstrated efficacy for the prevention of migraine. UB-313, a vaccine designed to stimulate the production of endogenous antibodies against CGRP, might provide an attractive new option to prevent migraine.

Design/Methods:
Immunogenicity studies were conducted in rodents and monkeys. Vaccine-induced serum antibodies were characterized for their binding and functional properties. Efficacy was assessed in a rat capsaicin model and toxicity was evaluated in a repeat-dose GLP study.

Results:
Studies in rodents and monkeys demonstrated that immunization with UB-313 induces robust anti-CGRP antibodies across species. Affinity purified antibodies from immunized animals were shown to bind human CGRP with high affinity (KD in the low pM range) and demonstrated a dose-dependent functional inhibition of CGRP (EC_{50} in the low nM range) in cell-based assays, indicating antibody properties comparable to marketed monoclonal antibodies. Off-target analyses indicated very high specificity of the anti-CGRP antibodies for human CGRP. Interestingly, antibodies induced by UB-313 demonstrate a stronger potency against human CGRP than rat CGRP, despite a single amino acid substitution between species. Importantly, immunization of rats with the murine version of UB-313 prevented the effects of capsaicin on dermal blood flow to a similar extent as treatment with Galcanezumab. Preclinical toxicology studies indicated that UB-313 was safe and well tolerated, with findings limited to injection site reactions. Splenocytes collected after immunization of rats with UB-313 were not responsive to stimulation with the CGRP peptide, suggesting that UB-313 safely overcomes immune tolerance.

Conclusions:
UB-313 has now advanced to clinical development: the ongoing Phase 1 trial is designed to assess safety, immunogenicity and target engagement (capsaicin-induced increase in dermal blood flow). As a potentially safe and effective immunotherapy against CGRP, UB-313 may represent an affordable and convenient strategy to prevent migraine.

Expansion of an Intronic FGF14 GAA Short Tandem Repeat in Late-Onset Cerebellar Ataxia

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Objective:
To report on a novel autosomal dominant intronic GAA repeat expansion in the first intron of the fibroblast growth factor 14 gene (*FGF14*) causing late-onset cerebellar ataxia (LOCA).

Background:
LOCAs have until recently largely resisted genetic diagnosis. Contributing to this diagnostic gap is that non-coding structural variations, such as repeat expansions, are not fully accessible to standard short-read sequencing analysis.

Design/Methods:
We performed whole-genome sequencing on six cases from three large French-Canadian families with unsolved autosomal dominant LOCA and identified a candidate GAA repeat expansion in the first intron of *FGF14*. We determined a pathogenic threshold of $(GAA)_{\geq 250}$ following segregation study within the three families and tested for an association between the repeat expansion and disease in (1) 66 French-Canadian cases and 209 controls, and (2) 228 German cases and 199 controls. We also screened 20 Australian and 31 Indian cases for the repeat expansion.

Results:

We identified 128 cases carrying an *FGF14* GAA repeat expansion. The repeat expansion was present in 61%, 18%, 15%, and 10% of patients in the French-Canadian, German, Australian and Indian cohorts, respectively. We found a significant association between *FGF14* $(GAA)_{\geq 250}$ expansions and LOCA in the French-Canadian (OR=105.60, 95% CI=31.09-334.20; $p<0.001$) and the German (OR=8.76, 95% CI=3.45-20.84; $p<0.001$) series. Our data suggest that $(GAA)_{250\text{-}300}$ expansions are incompletely penetrant while larger expansions are fully penetrant. Cases developed a progressive cerebellar syndrome at an average age of 59 years. The ataxia was episodic at onset in 46% of cases. Downbeat nystagmus was observed in 42% of patients. Cerebellar atrophy was found in 74% of cases on MRI.

Conclusions:
This novel dominantly inherited intronic GAA repeat expansion in *FGF14* is a common cause of LOCA. Our study underscores the importance of identifying non-coding repeat expansions, because they likely account for some of the missing heritability in late-onset neurodegenerative disorders.

Atogepant for the Preventive Treatment of Migraine Among Participants With Episodic Migraine With Prior Treatment Failure: Results From the ELEVATE Trial

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Objective:
To evaluate the efficacy, safety, and tolerability of atogepant 60 mg once daily (QD) for the preventive treatment of episodic migraine (EM) in participants who have previously failed 2 to 4 classes of oral preventive medications.

Background:
Atogepant, an oral calcitonin gene-related peptide receptor antagonist, is approved for the preventive treatment of EM in adults in the United States.

Design/Methods:
ELEVATE was a randomized, double-blind, placebo-controlled trial conducted in Europe and North America. Adults (18-80 years) who previously failed 2-4 classes of conventional oral medications for migraine prevention and reported 4-14 monthly migraine days (MMDs) during the 28-day screening period were randomized to treatment with atogepant 60 mg QD or placebo. The primary endpoint was the change from baseline in mean MMDs across 12 weeks. Secondary endpoints included achievement of ≥50% reduction in MMDs, change from baseline in mean monthly headache days, and change from baseline in acute medication use days across 12 weeks.

Results:
A total of 309 participants were included in the efficacy analysis population (placebo: n=155; atogepant 60 mg QD: n=154). Of these participants, 56.0% failed 2 classes of oral migraine preventive medications and 44.0% failed ≥3 classes. A significantly greater decrease in MMDs (mean [standard error]) across the 12-week treatment period was observed with atogepant 60 mg QD (−4.20 [0.39]) vs placebo (−1.85 [0.39]; $P<0.0001$). All secondary endpoints demonstrated statistically significant improvement with atogepant vs placebo across the 12-week treatment period. The most commonly (≥5%) reported treatment-emergent adverse events (atogepant vs placebo, respectively) included constipation (10.3% vs 2.5%), COVID-19 (8.3% vs 9.6%), nausea (7.1% vs 3.2%), and nasopharyngitis (5.1% vs 7.6%).

Conclusions:
Atogepant 60 mg QD was efficacious, safe, and well-tolerated for the preventive treatment of EM in participants who previously failed 2-4 classes of oral preventive migraine medications.

Peripheral Blood Gene Expression Transcriptional Profiling Predicts Disease Progression in Primary Progressive Multiple Sclerosis

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Objective:

To develop blood transcriptome-based prognostic model to predict severe disease progression in untreated PPMS patients.

Background:

Accurate prediction of long-term disease outcome remains a challenge for patients with primary progressive multiple sclerosis (PPMS).

Design/Methods:

Peripheral blood samples of PPMS patients included in the placebo-arm of the ORATORIO clinical trial (NCT01194570), were subjected to RNA-sequence analysis by Illumina NovaSeq S2. We applied 2-levels cross-validation algorithm (www.partek.com) to predict 12-weeks confirmed disability progression (12W CDP) during 120 weeks follow up, and the percent of brain volume change (PBVC) at 24, 48 and 120 weeks of follow-up.

Results:

RNA samples from 65 PPMS patients, age 43.9±1.4 years, female/male ratio 21/44, baseline EDSS 4.5±0.2 were analyzed. Correct classification rate of the 37% of patients with 12W CDP was 90.8% (95% CI 80.6 – 100.0%) using a 10-gene classifier. Correct classification rates of 63%, 57% and 64% of patients with 24, 48 and 120 weeks of brain volume change respectively, was 74.0%, (95% CI 65.1% – 83.0%), 84.0%, (95% CI 75.1%-93.1%) and 82.9% (95% CI 73.8%-95.6%), respectively.

Conclusions:
Transcriptome data correctly predicts disability progression and brain volume change in untreated PPMS patients that could benefit from early treatment.

Efficacy and Safety of Continuous Subcutaneous ND0612 Infusion Compared with Oral Immediate-release Levodopa-Carbidopa in Patients with Parkinson's Disease and Motor Fluctuations. Results From the Phase 3 Multicenter, Randomized, Double-blind, Double-dummy BouNDless Trial

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Objective:

Determine the efficacy, safety, and tolerability of ND0612 versus oral immediate-release levodopa/carbidopa (IR-LD/CD) in patients with Parkinson's disease (PwP) experiencing motor fluctuations.

Background:

ND0612 is an investigational, continuous 24-hours/day subcutaneous infusion of levodopa/carbidopa.

Design/Methods:

Double-blind, double-dummy (DBDD), parallel-group clinical trial (NCT04006210). PwP on ≥4 oral LD/CD doses/day (≥400mg/day LD) and experiencing ≥2.5h of daily OFF-time underwent 4-6 weeks of open-label IR-LD/CD dose adjustment followed by 4-6 weeks of open-label ND0612 conversion with adjunctive oral IR-LD/CD as needed to optimize ND0612 regimens. Patients were then randomized (1:1) to 12-week DBDD treatment with either their optimized ND0612 or IR-LD/CD regimens. Primary efficacy endpoint was the change in ON-time without troublesome dyskinesia from self-report diaries.

Results:

Baseline characteristics of the 259 patients were balanced between groups. In the DBDD, the ND0612 regimen provided an additional 1.72h [1.08h, 2.36h] of ON-time without troublesome dyskinesia compared to IR-LD/CD ($p<0.0001$). Mean ON-time without troublesome dyskinesia increased in both arms while on ND0612 during conversion from 9.4h (both arms) at enrollment to 11.8h (ND0612) and 12.1h (IR-LD/CD). During the 12-week DBDD treatment, ON-time without troublesome dyskinesia was maintained in the ND0612 group (11.5h at endpoint) but decreased in the IR-LD/CD group (9.9h at endpoint). Significant treatment effects were also seen in the first four hierarchical secondary endpoints: OFF-time, MDS-UPDRS Part II, and global impressions by patients and clinicians (all $p<0.0001$). Infusion site reactions were the most reported adverse events (83.8% during conversion, DBDD: 57.0% for ND0612, 42.7% for IR-LD/CD). Discontinuation rates overall and due to adverse events in DBDD were 6.3% and 5.5% for the ND0612 group and 6.1% and 3.1% for the IR-LD/CD groups.

Conclusions:

In this study, treatment with ND0612 led to significant, clinically meaningful improvement in motor fluctuations and functional endpoints such as improved experiences of daily living vs oral IR-LD/CD and was well tolerated.

The Effect of Catheter Ablation on Cognitive Outcomes in Elderly Patients with Atrial Fibrillation: SAGE-AF

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Objective:
To cross-sectionally and longitudinally examine the association between catheter ablation (CA) and cognitive function among older patients with atrial fibrillation (AF).

Background:
It is believed that patients with AF have long-term cognitive deficits and decline due to alteration of the cerebrovascular hemodynamic profile. Therefore, treatment of the underlying arrhythmia should lead to less cognitive impairment in those who undergo catheter ablation.

Design/Methods:

Patients with AF ≥ 65-years-old were recruited into the SAGE (Systematic Assessment of Geriatric Elements)-AF study from internal medicine and cardiology clinics in Massachusetts and Georgia between 2016 and 2018. Cognitive function was assessed using the Montreal Cognitive Assessment (MoCA) tool at baseline, one-, and two years. Cognitive impairment was defined as a MoCA score ≤ 23. Multivariate adjusted logistic regression was used to associate the risk of cognitive decline and hemorrhagic events with CA versus medical management.

Results:

887 participants were included in this analysis. On average, the participants were 75.2 ± 6.7 years old, 48.6% women and 87.4% white non-Hispanic. 193 (21.8%) participants received a CA prior to enrollment and more frequently had an implantable cardiac device (ICD) (*45.6% vs 27.5%, $p < 0.001$*) and persistent AF (*31.1% vs 22.5%, $p < 0.05$*). Participants who had previously undergone CA were significantly less likely to develop cognitive impairment during the two-year study period (*aOR 0.64, 95% CI 0.46-0.88*) than those who were only medically managed. No significant differences in hemorrhagic/ischemic events were observed in patients who underwent CA vs. medical management. Furthermore, a subgroup analysis of patients treated with warfarin versus all other anticoagulants (OACs) did not reveal a significant effect on cognitive decline.

Conclusions:
Those who underwent CA in addition to medical management developed less cognitive impairment than medical treatment alone for atrial fibrillation.

Mitochondrial Dysfunction in Neuron-Derived Extracellular Vesicles and Brain Tissues of FXTAS Patients

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Objective:

The objective of this study was to develop biomarkers reflecting mitochondrial dysfunction in fragile X-associated tremor/ataxia syndrome (FXTAS) using plasma neuron-derived extracellular vesicles (NDEVs) from living patients and controls, and assess their biological validity in frozen brain tissues.

Background:

FXTAS is caused by premutations of the fragile X mental retardation 1 (FMR1) gene with 55-200 CGG repeats. Premutation carriers are at increased risk of developing intention tremor, ataxia, parkinsonism, and cognitive impairment with age. Mitochondrial dysfunction contributes to FXTAS pathogenesis.

Design/Methods:

We isolated plasma NDEVs by immunoaffinity capture targeting L1CAM from 8 FXTAS patients (stage 1-4) and 4 male controls and measured the quantity and activity of complex IV and V (also termed ATP synthase). Additionally, we processed frozen cerebellar and frontal cortex samples from a separate cohort of 8 FXTAS patients (stage 4-5) and 9 male controls and evaluated the same measures.

Results:

In NDEVs, FXTAS patients compared to controls had lower activity of complex IV (0.027 vs. 0.046 AU, p = 0.02) and ATP synthase (0.037 vs. 0.062 AU, p = 0.046), but also higher ATP synthase quantity (0.0024 vs. 0.0016 AU, p = 0.03). ATP synthase activity was negatively correlated with FXTAS stage (r = -0.613, p = 0.045). The cerebellum of FXTAS patients compared to controls had lower complex IV quantity (2.004 vs 9.226 AU, p = 0.005) and activity (0.191 vs. 0.604 AU, p = 0.01); and lower ATP synthase quantity (7.852 vs. 19.953 AU, p = 0.037). No differences were observed for frontal cortex.

Conclusions:

Quantitative and functional abnormalities in mitochondrial electron transport chain and ATP production are manifest in plasma NDEVs of FXTAS patients and correlate with disease severity. These abnormalities may be predominantly attributable to the cerebellum. Plasma NDEVs may provide biomarkers for FXTAS prediction and monitoring.

RELIEF-PHN1: A Phase 2, Double-Blind, Randomized, Placebo-Controlled Trial of LX9211 in the Treatment of Postherpetic Neuralgia Pain

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Objective:
To evaluate the efficacy and safety of LX9211 in postherpetic neuralgia (PHN)

Background:

PHN is a debilitating complication associated with Varicella zoster. The pain associated with PHN can last for months or years after the zoster rash has cleared. Often the available treatment options do not provide adequate pain relief, and these treatment options are associated with undesirable side effects including somnolence and peripheral edema.

LX9211 is a potent, small molecule inhibitor of adaptor-associated protein kinase 1 (AAK1) which is a novel, non-opioid target for the treatment of neuropathic pain (NP). In a recent Phase 2 study, RELIEF-DPN 1, once-daily oral administration of LX9211 significantly reduced NP in patients with painful diabetic peripheral neuropathy.

Design/Methods:

A multicenter, Phase 2, double-blind, randomized, placebo-controlled, parallel-group study was conducted evaluating the efficacy and safety of LX9211 in the treatment of PHN. Adults (≥18 years of age) with prior Varicella zoster skin rash and PHN pain persisting for ≥3 months after healing of the Varicella zoster skin rash who met all inclusion and no exclusion criteria were eligible for enrollment in this study. The primary outcome was change from baseline in Average Daily Pain Score (ADPS) based on the 11-point numerical rating scale.

Results:

Treatment with LX9211 resulted in consistent reduction in ADPS, compared to placebo, throughout the 6-week dosing period. This was statistically significant when measured across dosing period but did not reach significance at Week 6 primary endpoint. The adverse event profile in this study was consistent with that observed in the prior study in patients with DPN with dizziness reported as the most common adverse event. There were no serious adverse events or deaths reported in the study.

Conclusions:

Together with the successful RELIEF-DPN 1 study, this study supports further clinical evaluation of LX9211 as a novel, non-opioid treatment option for multiple neuropathic pain conditions.

Teriflunomide (Aubagio) Extends The Time To Multiple Sclerosis In Radiologically Isolated Syndrome: The TERIS Study.

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Objective:

This study aims to analyze the efficacy of teriflunomide (aubagio®) in extending the time to a seminal acute or progressive demyelinating event in a cohort of radiologically isolated syndrome (RIS) subjects from Europe and Turkiye.

Background:

RIS subjects present with MRI features typical for multiple sclerosis (MS) without clinical symptomatology suggestive of central nervous system demyelination. Earlier treatment intervention may prevent the onset of a first clinical event and reduce the risk of new lesion development on MRI, decreasing the risk of permanent neurological impairment. In 2022, the ARISE study (NCT027395420) demonstrated that treatment with dimethylfumarate resulted in >80% risk reduction in developing MS relative to placebo in RIS.

Design/Methods:

This Phase III study (NCT03122652) enrolled 124 subjects and randomized 89 who fulfilled the 2009 RIS Criteria. Study participants were randomized 1:1 to teriflunomide (14 mg daily) or placebo. The primary outcome measure was time to the first event from study entry. All MRI and clinical data were independently adjudicated. Standardized brain and spinal cord MRI studies and clinical events were performed at baseline and weeks 48 and 96.

Results:

Of the 89 randomized RIS subjects, 63 (70.8%) were female, mean age of 39.8 years, age at index MRI:38 y). 28 clinical events were detected during follow-up (PCB:20, teriflunomide: 8). Results from the unadjusted (HR=0.38,95% confidence interval (CI)=0.17-0.88, p=0.025) and adjusted (HR=0.34,95% CI=0.14-0.82, p=0.016) demonstrated the superiority of teriflunomide. Compared to placebo, the number of patients with Gd+ lesions (OR=0.31,95%CI:0.08-1.18, p=0.087) and the cumulative number of new or-enlarging T2 lesions (RR=0.69,95% CI=0.34-1.40, p=0.31) were reduced in the teriflunomide arm, even if the statistical significance was not achieved.

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Conclusions:

Treatment with teriflunomide resulted in an 62% risk reduction relative to placebo in preventing a first clinical event in participants with RIS. These data support early intervention with disease-modifying treatment during the presymptomatic phase of MS.

Continuous Delivery of Levodopa/Carbidopa Using the Intra-Oral DopaFuse System: A Safety, Tolerability, PK and Efficacy Trial

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Objective:

Assess the safety, PK, and efficacy of levodopa/carbidopa (LD/CD) delivered continuously by an intra-oral micropump (DopaFuse) compared with standard oral LD/CD.

Background:

It is well-established that continuous delivery of levodopa/carbidopa (LD/CD) is associated with significant improvement in ON time without troublesome dyskinesia and OFF time in advanced PD patients. The DopaFuse system attaches to a retainer and uses a propellant to deliver LD/CD continuously into the mouth, thereby avoiding the need for surgical procedures, cumbersome pumps, and the development of infusion site reactions.

Design/Methods:
16 patients participated in a 2-week, open-label trial. Patients were treated in clinic as follows: Day-1, usual dose of standard LD/CD; Day-2, continuous delivery of LD/CD with DopaFuse; Day-3, continuous delivery of LD/CD with DopaFuse after a single morning dose of standard LD/CD. Patients were sent home on Days 4-14 and treated with the same regimen as Day-3, and returned to clinic on Day-15. Levodopa PK was measured at 30-60min intervals for 12h on Days 1, 2, and 3. Motor state was evaluated at 30-min intervals for 12h on Days 1, 3, and 15.

Results:
In comparison to standard LD/CD treatment (day1), continuous intra-oral delivery was associated with significantly less variability in plasma levodopa as determined by fluctuation index ($P=0.01$ and $P<0.001$ on Day- 2 and Day-3 respectively) and Coefficient of Variation ($P=0.02$ and $P<0.001$ on Day-2 and Day-3 respectively). ON time without severe dyskinesia and OFF time on Day-3 and -15 each significantly improved with DopaFuse ($P<0.001$) as was UPDRS-part II at Day-15 ($P=0.016$). There were no dropouts and no clinically significant adverse events.

Conclusions:
Continuous delivery of LD/CD using the DopaFuse System was well tolerated. DopaFuse was associated with significantly less variability in plasma levodopa and significant improvement in measures of motor function and ADLs in comparison to treatment with standard intermittent LD/CD.

Eplontersen in Hereditary ATTR-polyneuropathy: Week 66 Final Analysis of the Phase 3 NEURO-TTRansform Study

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Objective:
To evaluate the final efficacy and safety analysis of eplontersen at Week 66 in patients with hereditary transthyretin amyloidosis with polyneuropathy (ATTRv-PN) in the phase 3, international, open-label NEURO-TTRansform study (NCT04136184).

Background:
ATTRv-PN is a rare, progressive, and debilitating disease caused by accumulation of amyloid fibrils composed of transthyretin (TTR) protein in multiple organ systems. Eplontersen, a ligand-conjugated antisense oligonucleotide that inhibits TTR protein synthesis, is being assessed in the NEURO-TTRansform study. Previously reported topline statistics established that the coprimary endpoints and key secondary endpoint were met at the prespecified Week 35 interim analysis. Eplontersen treatment resulted in significant reductions in serum TTR concentration and neuropathy impairment (modified Neuropathy Impairment Score +7 [mNIS+7]), and improved quality of life (Norfolk Quality of Life-Diabetic Neuropathy score [Norfolk QoL-DN]), compared with external placebo (from the NEURO-TTR study [NCT01737398]). Eplontersen treatment also demonstrated an acceptable safety and tolerability profile.

Design/Methods:
NEURO-TTRansform enrolled 168 adults with ATTRv-PN, defined by Coutinho Stage 1–2, a documented *TTR* sequence variant, and signs/symptoms consistent with polyneuropathy (Neuropathy Impairment Score ≥10 and ≤130). Patients were assigned 6:1 to eplontersen 45 mg subcutaneously every 4 weeks (n=144) or inotersen 300 mg once weekly (n=24) until the prespecified Week 35 interim analysis, after which all patients received eplontersen 45 mg subcutaneously every 4 weeks. All patients who received eplontersen were compared with an external placebo group from the NEURO-TTR study at Week 66. Coprimary efficacy assessments at Week 66 included serum TTR concentration, mNIS+7, and the Norfolk QoL-DN score. Safety and tolerability were also assessed.

Results:
Full results from the efficacy and safety analysis at Week 66 and Week 35 will be presented.

Conclusions:
Results from the final analysis at Week 66 will provide detailed longer-term data on the efficacy and safety of eplontersen in patients with Stage 1 or 2 ATTRv-PN.

Interim Results from the NEXUS Open-Label Registration Study on the Safety and Efficacy of Leriglitazone in the Treatment of Childhood Cerebral Adrenoleukodystrophy

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Objective:
To assess 24-week safety, efficacy and study continuation criteria in boys with cerebral adrenoleukodystrophy (cALD) treated with leriglitazone.

Background:
cALD is a rapidly fatal, X-linked neurodegenerative disorder characterized by inflammatory brain demyelination. Allogeneic and autologous hematopoietic stem cell transplantation (HSCT) may halt disease progression, but there is an unmet need for less invasive therapies that can be administered immediately upon lesion identification. Leriglitazone is a peroxisome proliferator-activated receptor γ agonist with potential for treating adrenoleukodystrophy.

Design/Methods:

This 96-week, open-label, multicenter study for European registration (NEXUS; NCT04528706) of once-daily oral leriglitazone has enrolled 17 boys (target: 13) 2–12 years old with cALD with or without gadolinium-enhancing lesions. The primary endpoint is the proportion of patients with clinically and radiologically arrested disease at week 96 (success criteria: one-sided 95% confidence interval [CI] > 10%). We present a prespecified 24-week interim analysis, including assessment of study continuation criteria (≥ 4/13 patients with arrested disease or lesion growth deceleration without clinical progression). Secondary endpoints include change from baseline in neurological function score (NFS) and Loes score (LS). Change from baseline in plasma biomarker concentrations is an exploratory endpoint.

Results:
Eleven patients were evaluable at week 24. Continuation criteria were met: all patients demonstrated lesion growth deceleration. All remained clinically stable (free of major functional disability and stable NFS). Five patients had arrested disease (45.5%, 95% CI: 13.9–68.4%). Median (range) change from baseline was 0.0 (0.0–1.0) for NFS and 0.0 (0.0–3.0) for LS. Neurofilament light chain concentrations stabilized in most patients. Matrix metalloproteinase-9 concentrations decreased in all patients. There were no severe adverse events, treatment-related serious adverse events or deaths.

Conclusions:
Leriglitazone was well tolerated, continuation criteria were met, and disease arrest or stabilization was demonstrated radiologically, clinically and via plasma biomarkers. LS changes were similar to those attained with HSCT-based therapies. Enrolment is ongoing.

Deoxycytidine/Deoxythymidine Combination Therapy Safety and Efficacy in Treatment of POLG-Related Disorders: Results After 6 Months of Treatment

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Objective:
Evaluate the safety and efficacy of the combination of enteral deoxycytidine and deoxythymidine (dC/dT) in treatment of patients with POLG-related disorders involving depletion of mitochondrial DNA (mtDNA).

Background:

POLG-related disorders are caused by pathogenic variants in *POLG*, encoding DNA polymerase γ (POLG). This enzyme is responsible for mtDNA replication and proof-reading; with enzyme dysfunction, there may be an increased rate of mtDNA mutations and reduction in total mtDNA. As a result, patients with POLG-related disorders may have a range of clinical manifestations, including epilepsy, encephalopathy, neuropathy, myopathy, ataxia, eye movement abnormalities, liver dysfunction, lactic acidosis, renal dysfunction, hearing loss, pancreatitis. There are presently no effective treatments for POLG-related disorders.

Design/Methods:

Phase II, single-centre, open-label trial of dC/dT for people with POLG-related disorders and other mtDNA depletion disease. Inclusion criteria are: pathogenic variant in *POLG* or other gene associated with mitochondrial DNA depletion, neurological dysfunction, capable of taking liquid orally or via nasogastric/gastrostomy tube.

Patients receive dC/dT in a 1:1 ratio, given enterally, divided in 3 doses/day, titrated to 400 mg/kg/day, for a 2-year treatment period. Patients are evaluated at baseline, 1-month, 2-month, 3-month, and 6-month, 12-month, 18-month, and 24-month timepoints. Outcome measures include: Newcastle Pediatric Mitochondrial Disease Scale (NPMDS), EEG, seizure diary, liver function tests, kidney function tests, CK, lactate, and growth differentiation factor 15 (GDF-15). The latter is a marker of severity of mitochondrial dysfunction.

Results:
We have 6-month treatment data for 11 patients, including 8 with POLG-related disorders. No significant adverse events attributed to the treatment. All POLG patients had improved or stable NPMDS scores. All caregivers of POLG patients reported clinical improvement, including cognition, alertness, and energy level. Serum GDF-15 has either remained stable or decreased; in some POLG patients, the response has been dramatic.

Conclusions:
dC/dT therapy appears safe and effective in treatment of POLG-related disorders involving mtDNA depletion.

MEGAbIT: The role of magnetoencephalography in assessment and diagnosis in mild traumatic brain injury

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Objective:

Can measuring brain wave activity differentiate those with mild traumatic brain injury (mTBI) from orthopaedic trauma controls (with no head injury), and healthy controls.

Background:
MEGAbIT, an MRC funded study (Clinical Trials reference: NCT03867513), combined magnetoencephalography (MEG) with ultrahigh-field MRI, to detect functional and structural neuroimaging abnormalities within two weeks of mTBI.

Design/Methods:
We recruited 41 participants within two weeks of an emergency department visit and assessed resting state and task specific MEG, followed by ultrahigh-field MRI including structural, susceptibility, and diffusion sequences. Participant reported symptom scales were completed at baseline, three, and six months. Two prospectively selected analyses of resting state MEG data were conducted: excess delta band activity, the most commonly reported MEG abnormality in the literature, and reduced beta band burst coincidence connectivity, as this has previously demonstrated abnormalities in sub-acute mTBI.

Results:
No significant difference was found in global mean delta power between the mTBI cohort and either control cohort. However, a reduction in beta band burst coincidence connectivity was observed in the mTBI cohort compared to the healthy control cohort ($Z=-2.612$, $p = 0.009$). This gave a sensitivity of 86% and a modest specificity of 51%. Half our mTBI cohort had persistent self-reported disability, consistent with large prospective registry studies. Susceptibility weighted imaging revealed only two mTBI participants with microhaemorrhages, their clinical course did not differentiate them from others in the mTBI cohort.

Conclusions:
Given the global prevalence of mTBI and the high levels of persistent disability it causes, there is an urgent need for neuroimaging tools that link to both the underlying neuropathology and reported symptoms. Our results suggest that mTBI impairs the dynamic coordination of neural network activity. This finding was more sensitive than structural ultrahigh-field MRI and requires further exploration.

First-in-Human Trial of NRTX-1001 GABAergic Interneuron Cell Therapy for Treatment of Focal Epilepsy - Emerging Clinical Trial Results.

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Objective:
Investigate whether implantation of human GABAergic interneurons (NRTX-1001) can lead to seizure control in drug-resistant mesial temporal lobe epilepsy (MTLE).

Background:

Implantation of human cortical-type GABAergic interneurons in the hippocampus of mice with kainate-induced mesiotemporal sclerosis can control focal seizures (Priest et al., 2021, AES poster 1.091), with over two-thirds of the cell-treated animals becoming seizure-free for the duration of the 9-month study without producing lethargy, memory deficits, or other dose-limiting toxicities. The interneuron cell therapy also reduced hippocampal damage and increased animal survival. Interneuron cell therapy offers a novel approach to the potential treatment of human focal epilepsy.

Design/Methods:
This is a first-in-human Phase I/II clinical trial (NCT05135091). Subjects have unilateral MTLE with hippocampal sclerosis and focal seizures refractory to drug treatment. Testing includes EEG, imaging, tests of memory, mood, and assessment of visual fields. Subjects receive immunosuppression beginning 1 week prior to surgery tapering after 1 year. Cells are implanted via stereotactic injection along the long axis of the hippocampus with intra-operative MRI imaging.

Results:

Two subjects have been enrolled and had cell implantation. Data are reported as of 31Dec2022. There have been no serious adverse effects. Subject #1 is 6 months out from dosing. Baseline seizure frequency was 32/month; post-surgery, there has been a >90% seizure reduction and the subject has been free of focal awareness-impaired seizures since month 1. Subject #2 is 2 months out from dosing and has moved from a baseline seizure frequency of 14/month to one reported seizure since surgery.

Conclusions:

This first-in-human study of NRTX-1001 GABAergic interneurons for focal epilepsy is underway, and preliminary results are encouraging.

MOG-IgA characterizes a subgroup of patients with central nervous system demyelination

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Objective:
To investigate the frequency and clinical features of immunoglobulin (Ig) A antibodies against myelin oligodendrocyte glycoprotein (MOG) in patients with central nervous system (CNS) demyelination and healthy controls.

Background:
The differential diagnosis of patients with seronegative demyelinating CNS disease is challenging. In this regard, mounting evidence suggests that IgA plays a role in the pathogenesis of different autoimmune diseases. Yet, little is known about the presence and clinical relevance of IgA antibodies against MOG in CNS demyelination.

Design/Methods:
We conducted an observational, retrospective, longitudinal, multicenter study measuring MOG-IgA in serum using a live cell-based assay. We included a total of 1345 patients with neuromyelitis optica spectrum disorder (NMOSD), other CNS demyelinating diseases, and multiple sclerosis (MS), as well as healthy controls (HC).

Results:

Of all patients double-seronegative for MOG-IgG and AQP4-IgG (84%), isolated MOG-IgA was identified in 6% of patients with NMOSD, in 2% of patients with other CNS demyelinating diseases, and in 1% of patients with MS but in none of the HC. The most common disease manifestation in MOG-IgA seropositive patients was myelitis, followed by more frequent brainstem syndrome (p=0.047), and infrequent manifestation of ON (p=0.02) compared to MOG-IgG patients. Among patients fulfilling 2017 McDonald criteria for MS, MOG-IgA was associated with less frequent occurrence of type II oligoclonal bands (OCBs) compared to MOG-IgG/IgA seronegative MS patients (p<0.0001). Further, events of demyelination in MOG-IgA positive patients were more often preceded by infections and/or vaccinations than in MOG-IgG patients.

Conclusions:
We identified MOG-specific antibodies of the IgA isotype in a distinct subgroup of patients, suggesting MOG-IgA as a novel diagnostic biomarker for patients with AQP4-IgG and MOG-IgG double-seronegative CNS demyelination.

A Randomized Trial Of Endovascular Thrombectomy Versus Medical Management For Ischemic Stroke With A Large Core Infarct On Non-contrast CT Or Perfusion Imaging

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Objective:
To evaluate efficacy and safety of endovascular thrombectomy (EVT) vs best medical care in patients with large ischemic stroke on non-contrast CT or perfusion imaging

Background:
Patients with large ischemic strokes on non-contrast CT or perfusion imaging represent a significant subpopulation and may benefit from endovascular thrombectomy. However, randomized evidence of efficacy and safety of EVT is not well-established in this population.

Design/Methods:
SELECT2 was a prospective randomized, adaptive open-label phase III multicenter international trial with blinded endpoint assessment. Primary eligibility criteria included ischemic stroke with a proximal occlusion in internal carotid artery or first segment of middle cerebral artery; 2) large ischemic core infarct on non-contrast 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 10^{-6} mm^2/s of 50 ml or larger) 3) EVT feasible within 24 hours of when patients were last known to be well. Enrolled patients were randomly assigned to receive EVT + best medical care or best medical care only. The primary outcome of the trial was a shift in the distribution of modified Rankin Scale scores measuring disability status at 90-day follow-up. Key secondary outcomes include functional independence (mRS 0-2) and independent ambulation (mRS 0-3). Safety was assessed using symptomatic ICH and mortality.

Results:
Enrollment occurred at 31 centers across North America, Europe, Australia and New Zealand. After 352 patients were enrolled, the data and safety monitoring board recommended stopping the trial due to crossing of pre-specified boundaries based on their review of the first 300 enrolled patients' outcomes.

Conclusions:
The trial results are embargoed and will be presented at 2023 AAN annual meeting.

Holter of Movement Provides the First Digital Outcome Qualified by a Regulatory Agency

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Objective:
To gather regulatory qualification as a primary endpoint of the 95th centile of stride velocity, a digital outcome obtained by a wearable device. The context of use is ambulant patients with Duchenne Muscular Dystrophy

Background:

Quantifying movement disorders is challenging, as clinical condition of patients fluctuates and as these assesments can be subjective and poorly sensitive to change.

Magneto-inertial technology allows to reconstruct precisely strides in 3D with centimetric performance. This allows a precise and objective quantification of ambulation and gait of patients in their environment.

Design/Methods:

We have developed a wearable device to measure patients' movements continuously and accurately in the uncontrolled environments of everyday life and a platform of clinical outcomes to summarize data into clinically meaningful indicators.One of these outcomes, the 95th centile stride velocity (SV95C), represents the 5% most rapid strides performed by a patient over a span of at least 50 hours.

SV95C properties were studied in 125 ambulant patients with Duchenne, aged 5 to 14 years, from 6 different natural history studies and clinical trials and from patients attending routine clinic appointments.

Results:

The median error of stride velocity in comparison with gold standard motion capture was measured with 0.01 cm/s precision. The reliability of the SV95C measured during a > 50h period was 0.97. Compliance rate in uncontrolled environment was over 85%. The clear and rapid sensitivity to positive change in patients given steroids, as well as sensitivity to negative changes in patients from natural history significantly outperformed hospital-based assessments such as 6 minutes-walking-test.

Conclusions:

On January 23rd 2023, the SV95C (Stride Velocity 95th centile) received positive opinion by the European Medical Agency to become a qualified primary endpoint for ambulant patients living with Duchenne Muscular Dystrophy, opening the way to public consultation. A similar application is ongoing at the FDA.

Topline results of the PROOF-HD pivotal phase 3 trial: PRidopidine's Outcome On Function in Huntington Disease

Y Paul Goldberg[1], Ralf Reilmann[2], Andrew Feigin[3], Anne Rosser[4], Sandra Kostyk[5], Yael Cohen[1], Elena Berelovich[1], Michal Geva[1], Michael R Hayden[6]
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Objective:
To evaluate efficacy and safety of pridopidine 45 mg bid on clinical progression of Huntington's disease (HD) as measured by Total Functional Capacity (TFC).

Background:

Pridopidine is a well-tolerated, oral small molecule selective S1R agonist. Human PET imaging demonstrates selective and robust S1R occupancy by pridopidine at the clinically relevant dose (45 mg bid). In preclinical models, S1R activation by pridopidine restores mitochondrial-associated ER membrane (MAM) integrity and improves downstream cellular pathways impaired in HD, leading to neuroprotection.

In the exploratory PRIDE-HD Phase 2 trial, pridopidine 45 mg bid demonstrated a beneficial effect vs placebo (Δ0.87, p=0.0032) on TFC at Week 52 (pre-specified exploratory endpoint). Post-hoc analysis shows this effect is driven by mild to moderate HD patients (TFC7-13, Δ1.16, p=0.0003), and that TFC maintenance is associated with annual stabilization of plasma NfL levels (Δ from baseline in log2 pg/mL NfL -0.06 vs. +0.1 in placebo).

Design/Methods:

PROOF-HD is a multicenter, global double-blind, placebo-controlled, Phase 3 trial assessing pridopidine 45 mg bid in HD patients (TFC 7-13). Primary endpoint is mean change from baseline to week 65 in TFC. Secondary endpoints include change to week 65 in composite UHDRS (cUHDRS), proportion of patients with no TFC decline and changes in Q-Motor and Total Motor Score. Plasma neurofilament level is an exploratory endpoint.

Results:
PROOF-HD completed enrollment of 499 patients ahead of schedule in October 2021. As of January 12th, 2023, low dropout (42/499, 8.4%) is consistent with pridopidine's favorable tolerability and safety profile. In July, 2022, an independent safety monitoring committee (SMC) reviewed all unblinded safety data and concluded that no safety signals of concern emerged. SMC recommended continuation of PROOF without modification.

Conclusions:
At the time of abstract submission, PROOF-HD is still ongoing. Top line results are expected mid-April 2023 and will be presented.

ACHIEVE Trial, a Randomized, Placebo-Controlled, Multiple Ascending Dose Study of DYNE-101 in Individuals with Myotonic Dystrophy Type 1 (DM1)

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Objective:
To evaluate DYNE-101 in adults living with myotonic dystrophy type 1 (DM1).

Background:

DM1 is a severe neuromuscular disease caused by expanded CUG triplets in the dystrophia myotonica protein kinase (*DMPK*) RNA, which sequester splicing proteins into toxic nuclear foci resulting in a spliceopathy that ultimately drives disease progression. As there are no available disease-modifying therapies, treatment of DM1 is limited to symptom management.

The FORCE^{TM} platform was developed to overcome limitations of oligonucleotide delivery to muscle by harnessing the expression of transferrin receptor (TfR)1 on muscle cells. DYNE-101 is a TfR1-targeting antigen-binding fragment conjugated to a gapmer antisense oligonucleotide (ASO) that targets nuclear *DMPK* RNA. In preclinical models, DYNE-101 had a favorable safety profile and was shown to reduce mutant *DMPK* RNA, foci formation, and correct splicing defects, suggesting a potential effect in individuals with DM1.

Design/Methods:

ACHIEVE is a randomized, double-blinded, placebo-controlled, multiple ascending dose (MAD) Phase 1/2 study assessing safety, tolerability, pharmacodynamics, efficacy, and pharmacokinetics of DYNE-101 administered intravenously to adults with DM1 aged 18-49 years (NCT05481879). The study consists of three periods: MAD/placebo-controlled (24 weeks), open-label extension (OLE, 24 weeks), and long-term extension (LTE, 96 weeks). The primary outcome is the number of participants with treatment-emergent adverse events. Change from baseline in splicing index in skeletal muscle is a secondary outcome.

Results:

ACHIEVE will enroll ~64 participants in 4 cohorts of ascending doses of DYNE-101 (1.8, 3.4, 6.8, and 10.2 mg/kg approximate ASO equivalent doses). Participants in the 1.8 and 3.4 mg/kg DYNE-101 cohorts will be dosed every 4 weeks. Participants who receive 6.8 and 10.2 mg/kg DYNE-101 will be dosed every 4 or 8 weeks. All participants will receive the highest safe and tolerable dose of DYNE-101 during the OLE and LTE periods.

Conclusions:

The ACHIEVE study will inform further clinical development of DYNE-101 for the treatment of DM1.

Effects of EDG-5506, a Fast Myosin Modulator, on Proteomic Biomarker Profile of Muscle Damage in Adults with Becker Muscular Dystrophy (BMD)

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Objective:

ARCH is a 24-month Phase 1b open-label study designed to assess safety and PK with EDG-5506 in adults with BMD. Effects of treatment on biomarkers and function were also measured.

Background:

Fast (Type II) muscle fibers are affected early and disproportionately in dystrophinopathies. EDG-5506 is an investigational product that modulates fast skeletal muscle myosin and in animal models decreased muscle damage biomarkers and fibrosis while increasing muscle strength and activity.

Design/Methods:
12 ambulatory participants with BMD aged 20-46y received daily oral doses of 10-15 mg EDG-5506 for 6 months.

Results:

EDG-5506 was well tolerated without serious adverse events, withdrawals, or dose modifications. Most common adverse events were dizziness and somnolence (n=3 participants each), typically at initiation of dosing and self-resolving within a few days. Creatine kinase (CK) decreased by a mean of 40% from baseline to 6 months and fast skeletal muscle troponin I (TNNI2) decreased by 75% at last measurement (both $p<0.01$), while NSAA increased from baseline (4-31) by a mean +0.5 versus an expected decline of -0.6 (natural history data: Bello 2016, Van der Velde 2021). Plasma proteomics, measured with the 7K Somascan® Assay platform confirmed decreases in CK and TNNI2; further over 6 months there was evidence of progressive change in inflammatory proteins toward a profile of unaffected individuals.

Conclusions:

EDG-5506 was well tolerated up to 6 months of dosing with consistent reductions in biomarkers of muscle damage demonstrating target engagement. Proteomic profiles following treatment showed not only rapid and sustained improvements in proteins characteristic of muscle damage but also longer term changes in inflammatory proteins towards levels measured in unaffected individuals. This was associated with trends toward improvements in function compared to the expected natural history trajectories. Phase 2 trials in BMD and DMD are ongoing.