with the presumed mechanism of action of SAGE-718 as an NMDA-PAM, which supports the hypothesis of functional engagement of the NMDA receptor. These data, in addition to safety data collected to date, support further investigation of SAGE-718 in disorders characterized by hypoactivity at the NMDA receptor.

Keywords: SAGE-718, NMDA Receptor, Positive Allosteric Modulators, Biomarker

Disclosure: Sage Therapeutics, Consultant, PTC Therapeutics, Consultant, Perception Neuroscience, Consultant

M145

US-Latin American Initiative for Genetic-Neural-Behavioral Interactions in Human Neurodegenerative Research

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Background: This 5-years proposal fosters a Consortium with support from multiple partners aimed to combine genomic, neuroimaging and behavioral (clinical, cognitive, socioeconomic) data to improve dementia characterization in Latin American Countries (LACs) and identify novel inroads to treat neurodegeneration in diverse populations. We propose an innovative, harmonized, and cross-regional approach on two of their most prevalent neurodegenerative disorders: Alzheimer's disease (AD) and frontotemporal dementia (FTD). We are slotted to secure R01 funding (US-South American initiative for genetic-neural-behavioral interactions in human neurodegenerative research) that will support a basic platform anchored in Argentina, Brazil, Colombia, and Peru, that is supplemented with clinical research expertise from the University of California, San Francisco (UCSF), genomics expertise from the University of California, Santa Barbara, and bioinformatics expertise from HudsonAlpha. We now seek to extend this proposal to collaborators in Mexico and Chile. We also wish to assess novel families across LAC via the Latin America and Caribbean consortium on Dementia (LAC-CD). In addition to the R01 strategy based on patients with familial and sporadic presentations tested for genetic risks (risk scores), it would also support recruitment of AD and FTD families with an autosomal dominant-like presentation from the LAC-CD. In this expanded framework, we would first screen all patients for known AD/FTD/ALS genes and then, for those who screen negative for known genetic causes of disease, we will perform whole-genome sequencing (WGS) for gene discovery. We will establish a network of AD and FTD families and clinicians/researchers, enabling large-scale research to identify novel genetic and SES contributions to AD and FTD in diverse populations. Our long-term goal is to identify the unique genetic and SES factors that drive AD and FTD presentation in LAC relative to the US, including risk factors, cognitive profiles and brain imaging.

Methods: To this end, we will establish a first-in-class cohort anchored in six LAC (Argentina, Chile, Colombia, Brazil, Mexico, and Peru), compared to US samples (totaling > 4200 participants, including 2100 controls, 1050 AD patients, and 1050 FTD patients). We will couple standardized clinical assessments with innovative analytical techniques to account for heterogeneity in these diverse populations. By combining standardized genetic, neuroimaging, and behavioral (cognitive and SES) measures, we will test the underlying hypothesis that there are unique risk factors for AD and FTD in LAC (e.g., genetic risk factors enriched in LAC populations; underlying cognitive and neural vulnerability due to SES) compared to US populations.

Results: In this context, we will pursue the following Specific Aims:

Aim 1: To establish genetic contributions to AD and FTD in diverse LAC cohorts (Tier 1 study, with larger sample size than Tier 2). By elucidating the genetic substructure and familial contributions to AD and FTD in LAC relative to the US, we will be able to identify proper populations for replication of our genetic findings. By assembling this large cohort, we will also be well positioned to establish a LAC-specific polygenic risk score (PRS) for predicting AD and FTD risk in future samples.

Aim 2: To elucidate the impact of SES on clinical, cognitive, and brain imaging signatures in LAC and the US. (Tier 2 study-comprehensive imaging and cognitive evaluation in a subset of Tier 1). To compare patients across regions, we need to establish standardized neurocognitive measures and understand how SES impacts the manifestations of dementia in LAC.

Aim 3: To determine whether genetic risk and SES yield better discrimination between LAC and US patients as compared with other cognitive, neuroimaging, and clinical variables (Tier 1 & 2). To date, no study has sought to establish which potential predictors prove more sensitive to discriminate between LAC and US patients. In particular, although genetic risk and SES (Aims 1 and 2) have the potential to robustly differentiate between such samples, no study has explored their role, let alone as compared to other multimodal factors. To address this issue, we will apply data-driven machine-learning analysis to determine top factors that best discriminate patients in LAC from those in the US. Multimodal measures from controls of each country will be used for population-specific normalization of patient data. We hypothesize that the top features, better discriminating LAC from US patients will be related to SES and genetic risk (e.g., standardized PRS) in comparison to other variables (clinical, cognitive, and imaging measures).

Conclusions: The expected outcome of this study is a large Latin American cohort of harmonized, well-characterized AD and FTD patients and controls (Fig 1). Positive impacts of this work include a better understanding of genetic and SES contributions to neurocognitive manifestations of dementia and identification of novel targets for risk reduction and disease prevention in LAC. Our large multimodal, cross-sectional study will enable clinical assessment of understudied patient groups, extend and harmonize existing data sets, prompt the development of novel measures, and inform future work on the clinical value of combined multimodal profiles to predict disease presentation and progression in longitudinal studies of diverse populations.

Keywords: Neurodegenerative Disease, Genetics, Multimodal Imaging, Cognition, Machine Learning

Disclosure: Nothing to disclose.

M146

Irritability and Aggression in Huntington's Disease: A Phase 2 Exploratory Clinical Trial With a Novel Vasopressin 1a Antagonist, SRX246

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Background: Irritability and aggression are common in Huntington's Disease (HD) patients. These symptoms are highly distressing, adversely impact daily life, and often result in institutionalization. Effective treatments are unavailable and we need well-validated scales for measuring changes in these symptoms to develop these drugs. This Phase II clinical trial in individuals with HD (n = 106), Safety and Tolerability of SRX246 In Irritable/Aggressive Subjects with Huntington's Disease (STAIR; NCT02507284), rigorously evaluates the tolerability of a new drug, SRX246; provides additional safety data; and explores rating scales for the assessment of changes in these symptoms. The test drug, SRX246, is a first-in-class vasopressin 1a receptor antagonist. It exhibits high affinity and selectivity for its target, has a strong safety profile in healthy volunteers and other clinical trials, and excellent pharmacokinetics. Preclinical pharmacology and an experimental medicine fMRI study showed that SRX246 has CNS effects after oral administration and modulates brain circuits involved in responses to stimuli that elicit aggression/fear. In a Phase 2 Exploratory trial for the treatment of Intermittent Explosive Disorder, SRX246 was well tolerated, no serious adverse events were reported, and exploratory analyses revealed statistically significant differences favoring SRX246 in key clinical outcome measures. These findings suggested that SRX246 might have beneficial effects on the irritability/aggression seen in HD patients.

Methods: STAIR was a 3 arm, multicenter, randomized, placebo-controlled, double-blind, 12-week dose escalation study (22 sites in the NINDS NeuroNext network, total n = 106). Following eligibility determination, female and male participants were randomized to receive placebo or escalate from 80 mg (two weeks) to 120 mg (4 weeks), to a maximum of 160 mg twice daily for an additional 6 weeks. Participants had a Study Partner to assist with visits, taking study medication, and providing feedback about the subject's mood and behavior. Visits are either "in-person" or by "telephone". An eDiary (smart phone or tablet) prompted participants to take their capsules. The participants and study partners were also asked to answer daily questions about irritability, aggression, and other behaviors (electronic Patient Reported Outcomes, also recorded in the eDiary). Visits occurred at week 0 (baseline), 2, 4, 6, 8, 10, and 12. The primary objective was to evaluate the tolerability of SRX246. This was met through a non-inferiority test of the proportion of completers among the placebo group and each of the treatment groups. The study was powered to 80% with alpha=0.025. The secondary objective was to evaluate the safety of SRX246. The objective was met through a non-inferiority test of the proportion of participants with AEs or SAEs among the placebo group and each of the treatment groups. Exploratory analyses sought changes in irritability and aggression on various rating scales, including the Aberrant Behavior Checklist, Irritability Subscale; Cohen-Mansfield Agitation Inventory; Clinical Global Impression – Improvement; Problem Behaviors Assessment – short form; Irritability Scale; Caregiver Burden Questionnaire; Huntington's Disease Quality of Life Measure, and eDiary Responses. The objective was to obtain critical data that can be used to plan future Phase 2b or 3 clinical trials.

Results: Participants in each group had similar demographics, features of HD, and baseline irritability measures. Eighty-two of the 106 participants randomized completed the trial on their assigned dose of drug. A one-sided exact-method confidence interval was used to reject the null hypothesis of inferior tolerability for each SRX246 dose group versus the placebo. Similar analyses ware used to test for differences in Adverse Events (AEs) and Serious Adverse Events (SAEs); these also showed no significant differences between the active and placebo arms. Most of the adverse events in the active arms of the trial were considered unlikely to be related to SRX246. A total of 200 AEs were reported (in 85 study participants) after receiving study drug or placebo. Of the 200 AEs, nine (5%) were classified as SAEs – in 9 participants. Of these, none were both related to study treatment and unexpected. Exploratory analyses of the scales and behavioral results are in progress.

Conclusions: SRX246 was well tolerated and safe in HD participants. The tolerability and safety profiles in this study are consistent with prior results obtained in a Phase 1 multiple ascending dose trial, an experimental medicine fMRI study, and a Phase 2 study in participants with Intermittent Explosive Disorder that also showed good tolerability and safety. These data indicate that SRX246 can move forward as a candidate to treat irritability and aggression in HD if the exploratory analyses suggest efficacy.

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Keywords: Huntington's Disease, Phase II Clinical Trial, Irritability/Aggression, Vasopressin 1a Receptor Antagonist

Disclosure: Azevan Pharmaceuticals, Inc., Stock / Equity, Azevan Pharmaceuticals, Inc, Consultant, Azevan Pharmaceuticals, Inc, Board Member

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24(S)-Hydroxycholesterol Levels are Decreased in Early Huntington's Disease and are Associated With Deficits in Several Cognitive Domains

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Background: 24(S)-hydroxycholesterol (24(S)-HC) is an endogenous, brain specific, cholesterol metabolite that acts as a positive allosteric modulator of the N-methyl-D-aspartate (NMDA) receptor. Alterations in plasma and/or brain levels of 24(S)-HC have been identified in several diseases, including Smith-Lemli-Opitz syndrome, Niemann Pick, Huntington's disease (HD), and some forms of dementia. Although a broad range of pathology and core symptomology is observed across these different disorders, all manifest some degree of behavioral, cognitive, and psychiatric symptoms. One important question to be addressed is whether 24(S)-HC is associated with these symptoms and which features are most directly associated with decreased glutamatergic tone.

Cognitive deficits are a hallmark of HD and precede the onset of motor impairments by decades. Previous work has established that levels of 24(S)-HC are decreased in plasma and brain in HD patients, suggestive of decreased NMDA receptor function. Here, we investigated the relationship between 24(S)-HC and cognitive performance in samples from TRACK-HD, a longitudinal biomarker study of pre-manifest and early stage HD.

Methods: Plasma samples from the TRACK-HD study (60 control; 60 Pre-HD; 60 HD) were analyzed for 24(S)-HC via liquid-liquid extraction and analyzed with LC-MS/MS. Regression analysis was then performed between oxysterol levels and performance on a number of cognitive and motor endpoints.

Results: We found that levels of 24(S)-HC positively correlated with several cognitive tasks including the Stroop test, Trails A and B, symbol digit modality and processing of negative emotion in the Eckman faces task across all years of the TRACK-HD study. Interestingly, 24(S)-HC levels were not correlated with motor performance tasks and associations were not found for other oxysterols (25 and 27 hydroxycholesterol) supporting a specific role for 24(S)-HC/ NMDA dysfunction in non-motor aspects of HD.

Conclusions: These data support a critical role for NMDA receptor function in cognitive performance in Huntington's disease. We are currently evaluating the safety and tolerability