Introduction

- Nearly 25% of total body cholesterol resides in the central nervous system (CNS), where it is the principal component of myelin.1
- Lack of blood brain barrier permeability requires the conversion of cholesterol to 24(S)-hydroxycholesterol (HC) by the brain specific enzyme CYP46A1,2,3
- 24(S)-HC is a potent endogenous positive allosteric modulator (PAM) of the N-methyl-D-aspartate (NMDA) receptor.4
- 24(S)-HC is reduced in both plasma and brain tissue across Huntington disease (HD) stages.5,6
- Importantly, SAGE-718, an investigational, proprietary NMDA positive allosteric modulator, demonstrated an improvement in cognitive performance in a Phase 1 healthy volunteer study.7
- We examined correlations between plasma levels of 24(S)-HC and cognitive measures in TRACK-HD, a longitudinal observational study of biological and clinical manifestations of HD.8

Conclusions

- Our data support a role for 24(S)-HC in cognitive processes in HD and suggest that NMDA hypofunction may contribute to cognitive impairment in HD.
- The associations do not appear to be driven solely by neurodegenerative processes, and the associations are specific to 24(S)-HC (No associations were observed with 25-HC or 27-HC; data not shown).
- SAGE-718, an investigational NMDA positive allosteric modulator, is currently in clinical development for HD (phase 1).

Methods

- Plasma samples were collected over 4 years as part of the TRACK-HD study.
- Plasma samples were extracted using liquid-liquid extraction (oxysterols) or protein precipitation (cholesterol) and analyzed via liquid chromatography-tandem mass spectrometry.
- 24(S)-HC, 25-HC, and 27-HC were profiled and normalized (for 25-HC and 27-HC) to total cholesterol.
- Each oxysterol was then correlated across 19 cognitive and 23 neuropsychiatric endpoints within the year 2 samples (hypothesis generation).
- Those endpoints that were significantly correlated with oxysterol levels within year 2 were then tested against samples from years 1, 3, and 4 (hypothesis testing).
- A mixed model for repeated measures was applied, with change from baseline in each cognitive assessment test score as the response variable and treatment, visit, visit-by-treatment interaction as fixed effect, baseline as covariate, and measurements within the same subject as repeated measures. Unstructured covariance structure was applied for the repeated measure.

Results

- TRACK-HD was a longitudinal study of biological and clinical manifestations of HD.
- We collaborated with CHDI to determine plasma levels of 24(S)-HC and correlate levels with performance on clinically relevant endpoints.

24(S)-HC Correlations After Cell Loss Correction

- 24(S)-HC correlations across endpoints after correcting for potential cell loss. 24(S)-HC levels remain robust after segregating the data on median age and grey matter volume.
- Data are represented as –Log P value of regression.

24(S)-HC Correlations Across TRACK-HD

- 24(S)-HC correlations in years one, three, and four of TRACK-HD.
- Strong relationships between 24(S)-HC and cognitive measures were present across the years of TRACK-HD.
- Data are represented as –Log P value of regression.

EFFECT OF SAGE-718 ON COGNITION: WORKING MEMORY AND PROBLEM SOLVING

- SAGE-718, an investigational, proprietary NMDA positive allosteric modulator, significantly improved executive functioning in a Phase 1, multiple ascending dose study in healthy volunteers.