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Topline results in Healey ALS Platform Trial with AbbVie – Calico eIF2B activator Fosigotifator

The Sean M. Healey & AMG Center for ALS at Massachusetts General Hospital announced topline results from Regimen F of the HEALEY ALS Platform Trial evaluating fosigotifator (ABBV-CLS-7262) in people living with amyotrophic lateral sclerosis (ALS). Fosigotifator, an eIF2B activator, is an investigational drug being developed by Calico Life Sciences LLC (Calico) in collaboration with AbbVie.

A total of 155 participants were randomized to the primary dose, 79 to the exploratory high dose, and 126 participants were in the shared concurrent placebo cohort which includes placebo participants within this regimen (76) combined with placebo participants from another concurrently enrolling regimen (50). The primary analysis was the comparison of the primary dose to the shared concurrent placebo cohort. There were also pre-specified analyses of the exploratory high dose group to the shared concurrent placebo cohort and each dose to the regimen-only placebo group.

At the primary dose, the trial did not meet its primary endpoint, evaluating ALS disease progression as measured by the ALS Functional Rating Scale-Revised (ALSFRS-R) and survival from baseline through 24 weeks or key secondary endpoints of respiratory and muscle strength.

At the exploratory high dose, endpoints of muscle strength, as measured by hand-held dynamometry (HHD) were different between the active and placebo groups in both upper and lower extremities. In the upper extremity muscles, the exploratory high dose treatment group declined 32% slower than the shared concurrent placebo cohort (nominal p =0.014) and 37% slower when compared to the regimen-only placebo group (nominal p=0.007). In the lower extremity muscles, the exploratory high dose treatment group declined 62% slower than both the shared concurrent placebo cohort (nominal p =0.037) and the regimen-only placebo group (nominal p=0.054). In addition, there was a potential signal towards slowing respiratory functional decline as measured by the slow vital capacity (SVC) in the participants taking the exploratory high dose.

Overall, fosigotifator was found to be safe and well-tolerated with no meaningful safety differences between doses. Treatment emergent adverse event (TEAE) rates were comparable between the shared concurrent placebo group (89.7%) and combined

fosigotifator group (90.6%). Similarly, 26.2% and 25.2% of participants experienced TEAEs which were considered treatment-related in the shared concurrent placebo group and the combined fosigotifator group, respectively.

“While the results of this regimen did not meet the trial’s primary or key secondary outcome measures for the primary dose at Week 24, the findings at the exploratory high dose on muscle strength in both upper and lower extremities and possibly in respiratory function suggest that this target and approach need additional investigation. We have additional pre-specified subgroup analyses and biomarker work pending from this regimen, as well as long term efficacy data from participants who continued in the active treatment extension period. We remain deeply committed to fully understanding the effects of fosigotifator in ALS, and will further evaluate the data before determining next steps,” says Merit Cudkowicz, MD, MSc, principal investigator and sponsor of the HEALEY ALS Platform Trial, director of the Sean M. Healey & AMG Center for ALS, chair of the Department of Neurology at MGH, and the Julieanne Dorn Professor of Neurology at Harvard Medical School. “Every step we take brings us closer to finding effective treatments. Our dedication to the ALS community is unwavering, and we will continue to explore innovative pathways in our research.”

“We would like to extend our sincere gratitude to our participants, investigators, and staff who dedicated their time and expertise to this regimen,” says Senda Ajroud-Driss, MD, Regimen F co-lead and Director, Lois Insolia ALS Clinic at the Les Turner ALS Center at Northwestern Medicine, and the Les Turner ALS Foundation/ Herbert C. Wenske Professor of Neurology at Northwestern University, Feinberg School of Medicine in Chicago, Illinois. “The trial has provided substantial clinical data so far around dosing and the upcoming biomarker data and subgroup analyses will contribute to future studies and help us better understand ALS.”

Source: **Press release Calico Life Sciences**