Initiation of the Phase 2/3 GAIN trial of COR388, a novel bacterial virulence factor inhibitor for the treatment of Alzheimer’s Disease based on Phase 1/2 safety, PK, biomarker, and efficacy data

Michael Detke, MD PhD¹, Casey Lynch¹, Leslie J. Holsinger, PhD¹, Shirin Kapur, PhD¹, Dave Hennings, PhD¹, Debasis Raha, PhD¹, Florian Ermini, PhD¹, Ursula Haditsch, PhD¹, Mark Ryder, DDS², Ira Goodman, MD³, Stephen Thein, MD³, Stephen Dominy, MD³

¹CorTexyme, S. San Francisco, CA; ²UCSF, San Francisco, CA; ³Bioclinica, Orlando, FL; ⁴Pacific Research Network, San Diego, CA

BACKGROUND

COR388 is a novel bacterial protein, (ie gingipain) inhibitor being developed for the treatment of Alzheimer’s disease (AD). The mechanism of action is based on the discovery of Porphyromonas gingivalis (P. g) in the brain and cerebral spinal fluid of AD patients. The levels of toxic proteins called gingipains from the bacterium correlate with tau and ubiquitin pathology in the brain.

Oral infection of mice with P. g results in brain colonization, increased production of Aβ42-43, inflammation, and loss of hippocampal neurons (Evandi et al, 2018). These effects were blocked by COR388, a small-molecule irreversible gingipain inhibitor (Dominy et al, 2019). COR388 was selected to progress to human trials.

PHASE 1 RESULTS

COR388 was well-tolerated in a 28-day treatment of older healthy volunteers, 28-day study in mild to moderate AD subjects, and a 28-day study in mild to moderate AD subjects 55-85.

For AD subjects, Major inclusion criteria included having probable mild to moderate AD, baseline MMSE between 14 and 25, screening MRI compatible with AD, and no other cause of dementia. Subjects received 50 mg of COR388 or placebo q12 hr for 28 days as outpatients and returned to the clinic for safety assessments. CSF was collected at baseline and day 28. A cognitive test battery (CANTAB, Cambridge Cognition Ltd., UK) was designed to provide a broad evaluation of cognition. Winterlight’s software (Winterlight Labs, Toronto, CA) was used to generate descriptive and cognitive scores using acoustic and linguistic variables from participant’s description.

EXPLORATORY COGNITIVE TESTING

MMSE scores showed a trend of improvement from baseline and compared to placebo; the difference was not statistically significant (A) & (B); CANTAB memory composite of cognitive function showed a trend to benefit of COR388 treatment compared to baseline and compared to placebo (B); the difference was not statistically significant.

Winterlight speech and cognitive battery was used to assess the change from baseline in 35 speech variables. Improvement in the level of detail provided during the picture description was seen in the treatment group but not in the placebo group. Three speech measures significantly increased in the treatment group including use of omissions and subordinating conjunctions (C) in which COR388 vs. placebo remained significant after Bonferroni correction.

CONCLUSIONS

The gingipain hypothesis of Alzheimer’s disease, with P. g as an etiologic agent, is supported by scientific literature from multiple disciplines and several independent labs. COR388 is a promising drug for the treatment of AD with a novel mechanism of action. COR388 inhibits the Kgp gingipain protease secreted by P. g, essential for pathogen survival and virulence. COR388 is readily bioavailable after oral administration with a favorable PK profile and CNS penetration in humans, with target plasma concentrations for efficacy reached. COR388 was well tolerated and AD patients treated with COR388 for 28 days demonstrated significant reduction in several pharmacodynamic biomarkers including plasma RANTES and pathological ApoE Fragments in CSF. There was also a trend of improvement in some cognitive tests in AD patients treated with COR388, in contrast to subjects receiving placebo. Cortxyme is currently enrolling a 170-patient Phase 2/3 study of COR388 assessing the efficacy, safety, and tolerability of two dose levels of COR388 for a 48-week treatment period in subjects with mild to moderate Alzheimer’s disease. This potentially pivotal study is now ongoing.