Replication Trial To Confirm Reversal of Cognitive Decline with Bryostatin for Advanced Alzheimer’s Patients in the Absence of Memantine

Richard Thompson, PhD1; Lee Jen Wei, PhD2; Alan J. Tuchman, MD3; and Daniel L. Alkon, MD3
1Johns Hopkins University, Baltimore, MD, USA; 2Harvard University, Boston, MA, USA; 3Neurotrup, Inc., New York, NY, USA.

ABSTRACT

Background
Bryostatin, pre-clinically shown to induce neurogenesis and prevent neuronal death, is being evaluated in a double-blind, placebo-controlled randomized Phase IIb replication trial in patients with a disease stage of 20 μg of bryostatin or placebo to confirm reversal of cognitive decline in advanced Alzheimer’s disease (AD) patients in the absence of memantine, a 1:1 treatment allocation. Subjects on Memantine (SIB) in the previous phase of the study was previously shown to blindly sustain cognitive improvement observed in a recently published double-blind, placebo-controlled randomized Phase II trial (Stucky et al., 2019).

Methods
In the present confirmatory trial, each patient received two initial doses of study drug, bryostatin 20 μg in each arm separated by 1 week. It was followed by dose every 3 weeks; a total of 12 doses over 4 weeks. The primary endpoint is Severe Impairment Battery (SIB) score at 13 weeks versus placebo.

A pharmacokinetic study with Alzheimer’s patients demonstrated a peak activation by bryostatin of PKCε in the brain and a neutralization of the peak of brain PKCε blood levels.12,13 Furthermore, compulsive tests showed improvements in AD-patients with advanced disease.

RESULTS OF INITIAL PHASE 2 TRIAL

In a previous trial, we conducted a double-blind, randomized phase 2 trial, in which bryostatin was administered by intravenous infusions to patients with advanced Alzheimer’s disease for 12 weeks. Adult males 55-75 with cognitive deficits present at least one on the following: MCI, MCI-AD, or AD were included for this trial. Patients were randomized equally into the 20 μg bryostatin, 40 μg bryostatin or placebo treatment arms. 268 patients were enrolled at 27 clinical sites in the United States. Of these, 147 were randomized and 147 were treated with at least one dose of bryostatin. 135 patients were analyzed as the final Analysis Set (FAS) based on the modified intent to treat (mitit) principle. 135 of these randomized had 13 week outcome data, and were analyzed in the primary analysis. The mean (SD) SIB score for the 20 μg bryostatin and placebo randomized 1:1, stratified as in the first trial by disease severity of MCI-AD 4.0 ± 0.5 to 10.9, with a trial total of 92 patients. Patient participation has recently been completed in the current trial and data is now being thoroughly analyzed.

In both trials, the primary safety outcome was treatment emergent adverse events (TEAE). The primary efficacy endpoint was change in Severe Impairment Battery (SIB), a composite neurocognitive assessment using the Activities of Daily Living (ADL) scale. SIB scores were analyzed in the primary analysis.

In the present trial, the primary endpoint of the change in SIB at 13 weeks from baseline will be analyzed with ANCOVA and appropriate imputation methods. The results will be presented at a future congress, with the primary focus on the analysis of the primary endpoint in the current confirmatory trial.

METHODS AND MATERIALS

In a previous trial, we conducted a double-blind, randomized phase 2 trial, in which bryostatin was administered by intravenous infusions to patients with advanced Alzheimer’s disease for 12 weeks. Adult males 55-75 with cognitive deficits present at least one on the following: MCI, MCI-AD, or AD were included for this trial. Patients were randomized equally into the 20 μg bryostatin, 40 μg bryostatin or placebo treatment arms. 268 patients were enrolled at 27 clinical sites in the United States. Of these, 147 were randomized and 147 were treated with at least one dose of bryostatin. 135 patients were analyzed as the final Analysis Set (FAS) based on the modified intent to treat (mitit) principle. 135 of these randomized had 13 week outcome data, and were analyzed in the primary analysis. The mean (SD) SIB score for the 20 μg bryostatin and placebo randomized 1:1, stratified as in the first trial by disease severity of MCI-AD 4.0 ± 0.5 to 10.9, with a trial total of 92 patients. Patient participation has recently been completed in the current trial and data is now being thoroughly analyzed.

In both trials, the primary safety outcome was treatment emergent adverse events (TEAE). The primary efficacy endpoint was change in Severe Impairment Battery (SIB), a composite neurocognitive assessment using the Activities of Daily Living (ADL) scale. SIB scores were analyzed in the primary analysis.

In the present trial, the primary endpoint of the change in SIB at 13 weeks from baseline will be analyzed with ANCOVA and appropriate imputation methods. The results will be presented at a future congress, with the primary focus on the analysis of the primary endpoint in the current confirmatory trial.

CONTACT
Daniel L. Alkon, MD.
Email: dalcon@neurotrup.com

DISCUSSION

Replication of results of the initial confirmatory trial, bryostatin in the 20 μg improved SIB performance as compared to the placebo arm, suggesting that further study is warranted. The trial showed clinical benefit in providing symptomatic relief and delay of cognitive decline of patients with mild to moderate dementia. Further, there were consistent trends towards improvement in the SIB score of bryostatin as compared to placebo with a lack of efficacy due to a low power design of the trial that typically follows higher and/or lower levels of PKC activation.

In addition, the safety profile of exposure to bryostatin was similar between the bryostatin and placebo arms. The observation of no significant adverse events in the 20 μg bryostatin arm with more TEAEs as compared to those in the other treatment arms, suggests a lack of any further dose-response in this arm as compared to other study participants.

Secondary analyses of SIB over time in the patients without memantine demonstrated no significant benefit. The principle targets of bryostatin, PKC ε, are known to regulate multiple PKC ε functions and it is notable that the trial did not show any benefit. However, the non-significant finding was not surprising that the blockade of the NMDA receptor could often cause it not all of the bryostatin treatment effect.

CONCLUSIONS

Previous trials with neurotransmitter agonists and/or antagonists have demonstrated a lack of efficacy in advanced AD patients. A recent Aβ peptidic trial with prodromal and early AD patients also suggest a reduction in the risk of decline, although the trial was not continued in a follow-up trial. In contrast, evidence would suggest that bryostatin safely produced sustained cognitive improvement at the 20 μg dose at least four weeks after the termination of the dosing protocol.11 This sustained SIB score improvement was more evident in the absence of exposition to memantine. The confirmatory study currently underway will help further examine the efficacy of bryostatin in the absence of memantine to aid/and or reverse disease progression of advanced AD patients.

REFERENCES