INTRODUCTION

- CN156-016 was the first prospective randomized controlled trial in subjects with prodromal AD using entry criteria based upon clinical phenotypic features and CSF biomarker criteria consistent with AD.
- Avagacestat (BMS-708163), an oral γ-secretase inhibitor designed for selective inhibition of Aβ synthesis, was studied in prodromed AD in CN156-016 Phase 2 clinical trial.
- The purpose of this work was to assess volumetric MRI changes of Avagacestat-treated versus placebo subjects in whole brain, lateral ventricles, and hippocampus over the course of this multi-year study.

METHODS

Population

- 263 Prodromal AD subjects were selected, with the following inclusion criteria: MMSE 24 to 30, objective memory impairment, and Aβ-global score of 0.5 with a memory box score ≥ 0.5, CSF Aβ42 levels ≥200 pg/mL or total tau/Aβ42 ratio ≥ 0.39. Subjects were excluded if they met DMS-IV-TR criteria for dementia.
- All subjects underwent MRI examinations composed of a high resolution 3DT1 sequence in compliance with the ADNI protocol used across timepoints were considered.
- Subjects receiving matching placebo during the study were considered.
- All MRI data were sent for central processing (MP3D Electric) pulse sequences. All MRI data were sent for central processing to BioClinica once acquired.
- 20 additional subjects that met all clinical inclusion criteria but were not enrolled in the study were considered. T-tests were also performed in order to compare atrophy results between treated and placebo subjects (no correction for multiple comparisons was made).

RESULTS

- Mean volume loss for each structure of interest is reported in Table 1 and Figure 1. The results of the t-tests are shown in Figure 1.
- As expected, the amyloid-negative observational cohort subjects exhibited less atrophy compared to Prodromal AD subjects after 1 year of treatment (p<0.01).
- Volume loss was greater for Avagacestat than placebo-treated subjects at Weeks 24 and 56 for brain (p<0.01), ventricles (p<0.05) and hippocampus (p<0.001).
- At Week 104, the difference was not significant.

CONCLUSIONS

- Biomarker positive Prodromal AD subjects demonstrated higher brain, ventricular and hippocampal atrophy compared to biomarker negative subjects followed in an observational cohort.
- CSF biomarker criteria consistent with AD pathology can effectively be used to enrich clinical trials investigating AD.
- Similar to observations reported in clinical trials with other anti-amyloid treatments, Avagacestat was associated with higher atrophy compared to placebo (statistically significant at Weeks 24 and 56 but not at Week 104).

REFERENCES

- Whole brain atrophy and lateral ventricle enlargement were assessed using T1-weighted imaging with voxel-based morphometry [3,4].
- Hippocampal atrophy was assessed using the Hippocampal Boundary Shift Integral [4].
- Mean volume loss for each structure of interest is reported in Table 1 and Figure 1. The results of the t-tests are shown in Figure 1.
- As expected, the amyloid-negative observational cohort subjects exhibited less atrophy compared to Prodromal AD subjects after 1 year of treatment (p<0.01).
- Volume loss was greater for Avagacestat than placebo-treated subjects at Weeks 24 and 56 for brain (p<0.01), ventricles (p<0.05) and hippocampus (p<0.001).
- At Week 104, the difference was not significant.
- Biomarker positive Prodromal AD subjects demonstrated higher brain, ventricular and hippocampal atrophy compared to biomarker negative subjects followed in an observational cohort.
- CSF biomarker criteria consistent with AD pathology can effectively be used to enrich clinical trials investigating AD.
- Similar to observations reported in clinical trials with other anti-amyloid treatments, Avagacestat was associated with higher atrophy compared to placebo (statistically significant at Weeks 24 and 56 but not at Week 104).

Table 1: Whole brain, ventricular and hippocampal volume change (mL) for treated and untreated subjects at Weeks 24, 56 and 104

<table>
<thead>
<tr>
<th>Structure</th>
<th>Treatment</th>
<th>N</th>
<th>Baseline (mL)</th>
<th>Week 24 (mL)</th>
<th>Week 56 (mL)</th>
<th>Week 104 (mL)</th>
<th>95% CI</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hippocampal atrophy</td>
<td>Avagacestat</td>
<td>81</td>
<td>80 (107)</td>
<td>78 (108)</td>
<td>76 (104)</td>
<td>75 (101)</td>
<td>0.36</td>
<td>0.73</td>
</tr>
<tr>
<td>Placebo</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
</tbody>
</table>

**: p<0.05, **: p<0.01. n.s.: not significant.