STUDY DESIGN

At the conclusion of the screening period, eligible patients were randomly assigned in a 3:1 ratio to receive the antisense oligonucleotide drug ISIS 814907 (BIIB080) or placebo. Cohort A (low dose ISIS 814907 or placebo every 4 weeks) and Cohort C (high dose ISIS 814907 or placebo every 4 weeks) and Cohort D (low dose ISIS 814907 or placebo every 12 weeks) in the open-label LTE comprised the Treatment Evaluation (TE) Period and a 6-month Post-Treatment (PT) Period. Those enrolled in the placebo-controlled period of the Phase 1b multiple ascending dose (MAD) study of ISIS 814907 in patients with mild AD and the open-label LTE were eligible for participation in the Phase 2 study. Cohort A (low dose ISIS 814907 or placebo every 4 weeks) and Cohort C (high dose ISIS 814907 or placebo every 4 weeks) were part of the open-label LTE comprising a 12-month TE Period and a 4- or 6-month PT Period. Subjects were evaluated up to 1 year post-dosing by experienced investigators who were masked to treatment status.

RESULTS

The key exploratory endpoint was CSF total tau.

Characteristics of Patients at Baseline

| Cohort | N | Age (years) | CDR Sum of Boxes | MMSE Total Score | CSF Total Tau | p-tau Concentration
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</thead>
<tbody>
<tr>
<td>A</td>
<td>6</td>
<td>76.5±6.7</td>
<td>1.1±0.4</td>
<td>24.5±4.8</td>
<td>104±60</td>
<td>0.6±0.2</td>
</tr>
<tr>
<td>C</td>
<td>9</td>
<td>77.8±3.7</td>
<td>0.8±0.4</td>
<td>23.5±2.5</td>
<td>74±59</td>
<td>0.6±0.2</td>
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The CSF samples obtained during Screening and on Day 1 were analyzed and results averaged to serve as the baseline sample for CSF biomarker analysis.

Effect of ISIS 814907 (BIIB080) on CSF Concentrations of Total Tau and Phospho-Tau Protein

A: Effect of ISIS 814907 (BIIB080) on CSF Concentrations

- **Total Tau**: The decrease in total tau concentration is observed over time according to dose group.
- **Phospho-Tau**

B: Change from Baseline

- The percentage change from baseline over time for total-tau and phospho-tau concentration is shown.

Conclusions

• Only mild and moderate AEs were reported in MAD Part 1 following ITB administrations of the ASO drug ISIS 814907 (BIIB080) every 4 or 12 weeks (total of 4 and 2 doses, respectively) to adults with mild AD.
• ISIS 814907 treatment resulted in a time- and dose-dependent reduction in the concentration of CSF total tau and phospho-tau.
• This study demonstrated antisenese-mediated suppression of tau protein may be a feasible therapeutic approach for other tauopathies.