Biomarker Outcomes from the Phase 1b/2a Safety Trial of the Anti-Alpha Oligomer Drug CT1812 in Alzheimer’s Patients

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ABSTRACT

CT1812, the only therapeutic candidate demonstrated to displace Aβ oligomers from synaptic receptor sites and to displace the brain into the conformational fluid, restoring normal cognitive performance in aged transgenic mouse models of AD. Chronic treatment of aged transgenic mice with efficacious doses of CT1812 significantly reduced inflammatory protein expression in CSF, and normalized Alzheimer's disease-related protein expression in CSF and plasma as measured by LC-MS/MS. CT1812 appeared safe and well tolerated with multiple doses up to 560 mg/day in healthy elderly volunteers (ClinicalTrials.gov Identifier: NCT02070797).

Further, the clinical development of CT1812 was completed in mild to moderate Alzheimer’s patients to evaluate biomarker responses as well as safety (ClinicalTrials.gov Identifier: NCT03207857).

METHODS

A multi-center, double-blind, placebo-controlled parallel group study was performed to evaluate safety, tolerability and pharmacokinetics of three doses of CT1812 (0.3, 280, and 560 mg) or placebo (N = 4 or 5 patients/group) given once daily for 28 days to Alzheimer’s patients (MME: 18-28). Plasma and CSF protein expression were measured by LC-MS/MS in samples prior to dosing (Day 0) and at ending of dosing (Day 28) and were compared within each patient and between dosing groups.

RESULTS

LC-MS/MS analysis resulted in the identification and relative quantitation of 311 CSF proteins and 153 plasma proteins across all subjects. Changes in expression of specific proteins were observed in both CSF and plasma following treatment with study drug. Multiple proteins were upregulated in the CSF in response to drug. These proteins previously linked to AD and proteins involved in axon guidance/CSF development, all of which could be expected to increase with disease progression. The relationship between protein function and disease, and association with therapeutic target receptor software will be reported in detail, along with additional CSF outcomes including Aβ40, Aβ42, tau and p-tau.

CONCLUSIONS

Treatment of Alzheimer’s patients with study drug once daily for 28 days resulted in protein expression changes in plasma and CSF as measured by LC-MS/MS. Along with safety and clinical outcomes, the protein expression outcomes will help guide the future development of CT1812. Additional trial include an investigating phase I dose finding study with PET/CT to assess synaptic density after treatment with CT1812 and a longer term Phase II efficacy study.

METHODS

RESULTS

CSF: Treated (day 28 - Baseline) vs. Placebo (day 28 - Baseline)

<table>
<thead>
<tr>
<th>PROTEIN FUNCTION</th>
<th>Fold Change</th>
<th>p-value</th>
<th>rank p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>enzyme inhibitor</td>
<td>0.81</td>
<td>0.038</td>
<td>0.148</td>
</tr>
<tr>
<td>vitamin</td>
<td>0.91</td>
<td>0.029</td>
<td>0.011</td>
</tr>
<tr>
<td>gluconeogenesis</td>
<td>0.87</td>
<td>0.044</td>
<td>0.076</td>
</tr>
</tbody>
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Neurogranin was measured with a sandwich ELISA assay performed on CalBioChem. Western blot analysis was performed on BioLegend human brain tissue lysates.

Conclusions

1. No change in most biomarkers

In vitro studies: Neurogranin

<table>
<thead>
<tr>
<th>PROTEIN</th>
<th>concentration</th>
<th>IC50</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neurogranin</td>
<td>90 mg</td>
<td>260 mg</td>
<td>p = 0.025</td>
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</tbody>
</table>

RESULTS

38 proteins changed differentially in CT1812-treated vs. placebo patients (p ≤ 0.05, i.e., higher or lower expression vs. placebo)

Further, study with CT1812 is planned

BIOFLUID LC/MSMS ANALYSIS

<table>
<thead>
<tr>
<th>BIOFLUID</th>
<th>SCREEN</th>
<th>Day</th>
<th>Fold Change</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>CSF</td>
<td>Treated (day 28 - Baseline) vs. Placebo (day 28 - Baseline)</td>
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<td></td>
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</tbody>
</table>

CONCLUSIONS

CT1812 is safe and well tolerated across all doses, no SAEs

PK: Greater than 80% estimated brain receptor occupancy achieved at all doses (threshold needed to demonstrate efficacy in preclinical studies)

The concentrations of 30 CSF proteins changed differentially in the CT1812 treatment group versus placebo (p<0.05).

CSF synaptic damage markers decreased (neurogranin and synaptophysin), consistent with a positive synaptic effect and CT1812’s mechanism of action.

Further studies with CT1812 are planned

Clinical Trials on Alzheimer’s Disease Meeting 2017

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