Neurodegenerative diseases, such as Alzheimer’s Disease (AD), are in part caused by the breakdown of regulatory pathways designed to prevent aggregation and accumulation of disease-associated proteins.

Cellular protein quality control systems (e.g., the ubiquitin-proteasome system, the autophagy-lysosomal pathway, and the heat shock protein [HSP] systems) are subjected to stress response signals, which activate the intracellular quality control system to prevent or degrade misfolded or aggregated proteins.

Aberrant, misfolded, or aggregated proteins thus overwhelm cellular networks necessary for the proteasome system.

Epichaperomes form, connecting cellular networks necessary for degradation or aggregation pathways with maintaining or propagating neurodegenerative diseases.

Epichaperomes maintain and drive the pathologic cellular phenotype by stabilizing aberrant proteins, preventing their degradation and, in some cases, aiding in their aggregation.

Inhibition of epichaperomes by PU-AD restores protein degradation and rescues neuronal functions.

Epichaperomes are specific cellular localization complexes that support neurodegeneration and aggregation of aberrant proteins.

Epichaperome inhibition PU-AD is well tolerated and has favorable plasma PK and CSF exposure in the Phase 1 study in healthy volunteers and has entered a Phase 2 trial in AD patients.

PU-AD specifically targets epichaperomes in AD brain

PU-AD treatment results in reduced levels of ptau and restores spatial memory/learning in AD mice

Clinical Trial Design

Part 1: Single Dosing

Objective: To evaluate the safety and tolerability of single oral doses of PU-AD in healthy subjects.

Part 2: Multiple Dosing

Objective: To evaluate the safety, tolerability, and efficacy of multiple oral doses of PU-AD in healthy subjects over 48 weeks of age.

Part 3: Bioavailability Study

Objective: To determine the relative bioavailability of a single 60 mg dose of PU-AD administered as an oral tablet compared to an oral solution of PU-AD in healthy subjects.

Human Pharmacokinetics

PK Parameters of Oral Administration of 20 mg or 30 mg of PU-AD QD for 7 Days

<table>
<thead>
<tr>
<th>Dose (mg)</th>
<th>T1/2 (h)</th>
<th>Cmax (ng/mL)</th>
<th>AUC0-∞ (h*ng/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>20</td>
<td>3.5 (3.2)</td>
<td>560 (555)</td>
<td>4230 (4096)</td>
</tr>
<tr>
<td>30</td>
<td>2.9 (2.7)</td>
<td>845 (820)</td>
<td>5700 (5500)</td>
</tr>
</tbody>
</table>

PK Parameters of 30 mg PU-AD Oral Solution and Tablet

<table>
<thead>
<tr>
<th>T1/2 (h)</th>
<th>Cmax (ng/mL)</th>
<th>AUC0-∞ (h*ng/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>3.0 (2.8)</td>
<td>232 (219)</td>
<td>1708 (1589)</td>
</tr>
</tbody>
</table>

Conclusions and Future Directions

PU-AD is a novel epichaperome inhibitory drug that shows promising efficacy in animal models of AD.

Clinical trials are ongoing to evaluate the safety and efficacy of PU-AD in human subjects with AD.

In summary, the data suggest that PU-AD could be a novel therapeutic option for the treatment of AD.

Clinical trial data for PU-AD will be presented at upcoming neurological conferences.

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