Beagle Dog Studies for ANG1005, a Novel Antimicrotubule Agent that Targets the Brain

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INTRODUCTION

ANG1005 is an antimicrotubule agent that contains the sequence of amino acids responsible for receptor-mediated transport across the blood-brain barrier (BBB). The proprietary Engineered Peptide Compound (EPC) platform targets the density lipoprotein receptor (LRP) related protein (LRP) receptor family. ANG1005 has been tested in Sprague Dawley rats in safety and pharmacology studies.

In vitro Cytokine Study

The in vitro antiproliferative activity of ANG1005 has been tested in various breast cell lines. The IC50 values for ANG1005 were comparable to paclitaxel in most of the cell lines, data from this study are shown below.

<table>
<thead>
<tr>
<th>Cell Line</th>
<th>IC50 ANG1005 µg/mL</th>
<th>IC50 Paclitaxel µg/mL</th>
</tr>
</thead>
<tbody>
<tr>
<td>MCF-7</td>
<td>0.012</td>
<td>1.00</td>
</tr>
<tr>
<td>MDA-MB-231</td>
<td>0.007</td>
<td>1.00</td>
</tr>
<tr>
<td>H460</td>
<td>0.10</td>
<td>1.00</td>
</tr>
<tr>
<td>A431</td>
<td>0.036</td>
<td>1.00</td>
</tr>
<tr>
<td>T47D</td>
<td>0.039</td>
<td>1.00</td>
</tr>
</tbody>
</table>

METHODS

Toxicity Studies of ANG1005 were conducted in Beagle dogs and in Sprague-Dawley rats (Reference No. 2039).

Repeatability

Table 1 presents the toxicokinetic data for ANG1005 in beagle dog following a single 75 mg/m² bolus dose. The elimination phase of the recovery period.

Effects of ANG1005 on hERG currents from transfected HEK293 cells were tested. ANG1005 concentrations up to 25 µM did not result in significant inhibition on hERG full current density in these studies. Cells treated with ANG1005 suggest that ANG1005 targets the LRP receptors and enables access to the endocytic system.

The general non-receptor toxicity studies included standard endpoints such as mortality, clinical observations, toxicokinetics (TK), clinical pharmacology, pathology, body weight, organ weights, microscopic (and/or) histological examination.

The preclinical pharmacokinetic and toxicology studies for ANG1005 have been well characterized.

The results of the observed toxicity profile in ANG1005 is currently being tested in two Phase 1/2 clinical trials in brain cancer patients.

CONCLUSIONS

The toxicity profile of ANG1005 in Beagle dogs has been investigated in a series of intravenous pharmacology and toxicology studies. The toxicity profile of ANG1005 in Beagle dogs was demonstrated to be consistent in the in vitro and in vivo dose range. The toxicity profile of ANG1005 in Beagle dogs enabled access to the endocytic system.

The TK profiles of ANG1005 were similar at all dose levels, with no apparent gender differences. There were no treatment related fatalities for the 90 mg/m² dose toxicity studies. Data are shown in the following tables. ANG1005 is a clinical candidate for phase 2 trials. ANG1005 is a clinical candidate for phase 2 trials.

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