Background

ALD403 is a humanized, IgG1, and CCR5 antibody being developed for the prevention of migraine.

Objectives

The objective of this phase of a clinical trial was to evaluate the pharmacokinetics and pharmacodynamics of ALD403, a humanized anti-CCR5 antibody, administered once every 3-months via IV, SC, or IM routes in healthy subjects.

Methods

This study was performed in compliance with the International Conference on Harmonization (ICH) Good Clinical Practice (GCP) guidelines for clinical trials, was approved by an Independent Ethics Committee, and all patients were given informed consent prior to enrollment. The study was conducted at Nicolls Research Limited, Melbourne, Australia and registered on AusCTR (AUSCTRI-1261058053159).

Healthy female and male subjects aged between 18 and 65 years inclusive and greater than 30% respectively to topical capsaicin treatment relative to placebo were qualified to participate in the trial. The subjects were randomized (stratified by gender) to one of six treatment groups consisting of 12 participants each and scheduled to receive three different injections IV, SC, or IM routes on study days 1 and 84, with up to one injection containing either 100 mg (SC, IM) or 300 mg (IM) ALD403, and the remaining injections as placebo. (IV injections [1 mL] were administered over one hour; SC injections (1 mL) were made to the anterior abdominal wall. 8 injections (3 mL) were made to the anterior hip. 3 successive lateral muscles).

Results

ALD403 Pharmacokinetics

Pharmacokinetic Parameters (Tables 1 and 2, Figure 2)

- Mean Cmax values following the first IM administration of ALD403 were approximately dose proportional from 100 to 300 mg, and AUC was slightly greater than dose proportional.
- The V1 or V2 values ranged from 4.6 to 8.1 L, and the CL or CL/F values ranged from 4.7 to 8.1 L/h. These values indicate minimal extravascular distribution by ALD403 and relatively slow elimination from the plasma compartment.
- The half-life for ALD403 following the first dose administration ranged from 30.2 to 35.7 days.
- The absolute bioavailability for ALD403 following IV administration, 79% at 100 mg or 65% at 300 mg, was higher than that observed for SC administration, 74% at 100 mg, and 59% at 300 mg.
- Following the second dose of ALD403 on Day 84, the exposure, AUC(0-t), following 100 mg IM administration, was slightly higher, 10,366 ng/mlh, than 100 mg IV administration, 7,448 ng/mlh.
- The dose-normalized exposure to ALD403 following the second dose, AUC(0-t)/D, was higher for 300 mg administration when compared to all other groups.
- The accumulation ratio for trough ALD403 plasma concentration, Ctrough, was highest for 100 or 300 mg IM administration, 1.4, when compared to IV, SC, or IM. The accumulation ratio for exposure, AUC(0-t), was even higher for 100 or 300 mg IM administration, 1.4, when compared to IV or SC (both 1.1).

Table 1: Mean (SD) PK Parameters for ALD403 following 1st Dose

<table>
<thead>
<tr>
<th>Results/Dose</th>
<th>IV 100 mg</th>
<th>SC 100 mg</th>
<th>IM 100 mg</th>
<th>300 mg IM</th>
<th>Mean (SD) PK Parameters for ALD403 following 1st Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cmax (µg/ml)</td>
<td>(4.7)</td>
<td>(3.2)</td>
<td>(6.3)</td>
<td>(6.8)</td>
<td></td>
</tr>
<tr>
<td>Tmax (median)</td>
<td>0.05</td>
<td>6.0</td>
<td>5.0</td>
<td>4.5</td>
<td></td>
</tr>
<tr>
<td>AUC(0-t) [ng·h/ml]</td>
<td>15,805</td>
<td>12,408</td>
<td>13,111</td>
<td>42,767</td>
<td></td>
</tr>
<tr>
<td>Ctrough (ng/ml)</td>
<td>3.0</td>
<td>2.4</td>
<td>2.5</td>
<td>8.7</td>
<td></td>
</tr>
<tr>
<td>CL or CL/F (L/h)</td>
<td>(0.8)</td>
<td>(1.2)</td>
<td>(0.5)</td>
<td>(2.4)</td>
<td></td>
</tr>
<tr>
<td>V1 or V2/L</td>
<td>4.7</td>
<td>6.9</td>
<td>6.0</td>
<td>5.6</td>
<td></td>
</tr>
<tr>
<td>V1 or V2/L (F)</td>
<td>(0.6)</td>
<td>(2.4)</td>
<td>(1.2)</td>
<td>(1.2)</td>
<td></td>
</tr>
<tr>
<td>Half-Life (days)</td>
<td>6.6</td>
<td>6.3</td>
<td>6.1</td>
<td>5.8</td>
<td></td>
</tr>
<tr>
<td>% Absolute Bioavailability</td>
<td>N/A</td>
<td>75.0</td>
<td>79.0</td>
<td>85.0</td>
<td></td>
</tr>
</tbody>
</table>

Pharmacodynamics

- The pharmacokinetic and pharmacodynamic results provide support for further evaluation in later stage clinical trials of 100 mg ALD403 IV, SC, or IM, or 300 mg IM administration, once every 3-months.

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Conclusions

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