Introduction

ACT-280778 is a non-dihydropyridine, dual L- and T-type calcium channel blocker. In animal models, ACT-280778 potently increases coronary flow and reduces myocardial ischemic severity. Data from non-clinical studies (Actelion Pharmaceuticals Ltd., data on file) show that ACT-280778 is a potent anti-hypertensive agent with a long duration of action. It appears to have a low risk of inducing reflex tachycardia and should be studied for potential minimization of reflex tachycardia. The potential for reflex tachycardia was assessed in the non-clinical profile of ACT-280778. Further investigation of this compound in human subjects is warranted.

Objectives

The objectives of the study were to evaluate the safety and tolerability of ascending single oral doses of ACT-280778 in healthy male subjects at doses of 2, 5, or 15 mg in both fed and fasted conditions. The study was designed to evaluate the effect of ACT-280778 on heart rate, blood pressure, and the dose and the dose proportionality of PK parameters over a range of doses. ACT-280778 was administered to the same subjects (food effect group).

Safety and tolerability evaluation

Safety and tolerability were evaluated throughout the study at all dose levels. Subjects were monitored for adverse events (AEs), vital signs, laboratory, 12-lead ECG, and physical examination.

Methods

Study design

The study was a prospective, single center, randomized, placebo-controlled, single ascending dose study. Randomization was stratified by subject age on the basis of the ranking of body mass index (BMI) and an algorithm with alternatives (use of a maximum Emax model instead of a logistic regression model) was adopted to balance the PK and the safety of ACT-280778 in support of the study. Each subject participated in one treatment period (fasted) with the study drug, ACT-280778. In the food effect group, only the first 2 subjects of the sentinel group received 40 mg to determine whether it was safe to proceed with the study. ACT-280778 concentration (pg/mL) was measured at each protocol-specified time point by monitoring adverse events (AEs), vital signs, laboratory, 12-lead ECG, and physical examination.

Subjects disposition

In total, 20 subjects (18 male, 2 female, mean age 30 years, range 18-37 years) were enrolled in the study. Each subject participated in one treatment period (fasted) with the study drug, ACT-280778. In the food effect group, only the first 2 subjects of the sentinel group received 40 mg to determine whether it was safe to proceed with the study. ACT-280778 concentration (pg/mL) was measured at each protocol-specified time point by monitoring adverse events (AEs), vital signs, laboratory, 12-lead ECG, and physical examination.

Data analysis

The doses for the first two groups were fixed (2 and 5 mg) and the dose of 15 mg was selected to select the optimal dose as a lead-in for the next pharmacokinetics portion following Trial 1 and Trial 2 subjects. The doses for the next dose group were defined as the minimum of the median of the measured plasma concentration–time curve (AUC 0–∞) across all safety endpoints, but not exceeding 10 times the highest dose administered so far.

Results

Safety and tolerability

No indication of increased effect over time or tachyphylaxis. Overall, ACT-280778 appears to have a low risk of inducing reflex tachycardia and shows tissue disorders

<table>
<thead>
<tr>
<th>Pharmacokinetics</th>
<th>2 mg</th>
<th>4 mg</th>
<th>5 mg</th>
<th>8 mg</th>
<th>12 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>PK parameter</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cmax (pg/mL)</td>
<td>224</td>
<td>604</td>
<td>1020</td>
<td>1620</td>
<td>1968</td>
</tr>
<tr>
<td>T1/2 (h)</td>
<td>3.5</td>
<td>3.5</td>
<td>3.5</td>
<td>3.5</td>
<td>3.5</td>
</tr>
<tr>
<td>AUC 0–∞ (pg∙h/mL)</td>
<td>2368</td>
<td>5616</td>
<td>8904</td>
<td>14544</td>
<td>19268</td>
</tr>
</tbody>
</table>

Safety

A slight increase from baseline was observed for the PR interval and QTc interval, but normal range was observed for other ECG variables in all dose groups.

Summary and conclusions

A population PK model estimated that food reduced the absorption rate by 80% and increased the extent of absorption by 82%. PK parameters were characterized by high inter-subject variability.

Modeling and Simulation

Modeling and simulation were performed with NONMEM (J. J. Beckman and F. Yamanouchi, Nutley, NJ, USA) using the PK, PD, and safety data obtained in the study. A slight increase from baseline was observed for the PR interval and QTc interval, but normal range was observed for other ECG variables in all dose groups.

Figure 1 shows as an example the estimated relationship between concomitant food effect and extent of absorption, indicating that the extent of absorption was increased by 82% and the absorption rate by 80% in the presence of food. PK parameters were estimated with a range of values (Oujebo et al., 1997) and were used in the simulations. PK parameters were defined as the next dose to be administered. The quantification of risk and determination of the next dose were based on estimated probabilities and adaptation of the dose escalation step size (Oujebo et al., 1997). The PK profile of ACT-280778 was consistent with a once-daily dosing regimen. The dose selection in ACT-280778 study was based on safety pharmacology data

<table>
<thead>
<tr>
<th>Candidate (mg)</th>
<th>2 mg</th>
<th>4 mg</th>
<th>5 mg</th>
<th>8 mg</th>
<th>12 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maximum decrease from baseline in systolic blood pressure</td>
<td>15</td>
<td>30</td>
<td>45</td>
<td>60</td>
<td>75</td>
</tr>
</tbody>
</table>

Dose escalation

Dose escalation was started at 2 mg and increased by 4 mg increments up to 15 mg.

Figure 2a shows the distribution of maximum acceptable dose (MTD) with estimated probabilities that a candidate dose (0 to 100 mg in 5 mg increments) is clinically acceptable. Figure 2b shows the estimated maximum tolerated dose (MTD) for each simulation, the highest acceptable dose constituted the MTD. The estimated probabilities that a candidate dose (0 to 100 mg in 5 mg increments) is clinically acceptable. Figure 2c shows the distribution of maximum tolerated dose (MTD) for each simulation, the highest acceptable dose constituted the MTD. The estimated probabilities that a candidate dose (0 to 100 mg in 5 mg increments) is clinically acceptable. Figure 2d shows the distribution of estimated probabilities that a candidate dose (0 to 100 mg in 5 mg increments) is clinically acceptable.