PHARMACOKINETICS, SAFETY AND COGNITIVE FUNCTION OF OF RUPATADINE IN HEALTHY JAPANESE VOLUNTEERS

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Introduction

Rupatadine (Rup) is a second generation antihistamine which possesses affinity for H1-receptor and anti-platelet activating factor (PAF) activity [1]. The therapeutic doses of 10 mg and 20 mg are effective and well tolerated for the treatment of allergic rhinitis and chronic urticaria [2] with no side effects on cardiac repolarization [3] and central nervous system [4]. Rup is metabolised in the liver and CYP3A4 has been identified as the primary isozyme responsible for Rup’s metabolism [1]. This study in Japanese was performed in order to assess if the PK profile of Rup is similar to Caucasians.

Aims

This Phase I, randomised, placebo-controlled study with oral and multiple doses of Rup aimed:
- To assess the safety and tolerability of Rup following single and multiple oral doses administration to healthy Japanese subjects.
- To investigate the pharmacokinetics (PK) of Rup and its main metabolites desloratadine (UR-12790) and 3-hydroxylated desloratadine (UR-12788) and to assess the effect of Rup on cognitive function, EEG data analysis will be reported elsewhere.

Methods

Study Design

Twenty seven (27) healthy Japanese male and female subjects completed the study. Subjects were randomised to receive single daily oral doses of Rup 10, 20 and 40 mg or matching placebo (two subjects per dose level). All subjects received placebo on Day -1 and a single dose of Rup or placebo on Day 1 followed by once daily doses on Days 2-5.

Results

Mean pharmacokinetic (±SD) parameters for Rup, UR-12790 and UR-12788 following administration of single and multiple doses of Rup (10, 20 and 40 mg) in Japanese. Median (min – max) values are presented for tmax.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Compound</th>
<th>Rup 10 mg</th>
<th>Rup 20 mg</th>
<th>Rup 40 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cmax (ng/mL)</td>
<td>UR-12790</td>
<td>2.02±0.70</td>
<td>2.65±0.67</td>
<td>3.61±0.35</td>
</tr>
<tr>
<td>Tmax (h)</td>
<td>UR-12788</td>
<td>1.15±0.19</td>
<td>1.79±0.38</td>
<td>3.96±0.56</td>
</tr>
<tr>
<td>T1/2 (h)</td>
<td>UR-12790</td>
<td>0.67±0.20</td>
<td>1.00±0.16</td>
<td>0.87±0.17</td>
</tr>
<tr>
<td>T1/2 (h)</td>
<td>UR-12788</td>
<td>1.21±0.34</td>
<td>1.92±0.46</td>
<td>1.21±0.26</td>
</tr>
<tr>
<td>AUC0-24h (ng*h/mL)</td>
<td>UR-12790</td>
<td>4.20±0.30</td>
<td>4.95±0.15</td>
<td>4.22±0.35</td>
</tr>
<tr>
<td>AUC0-24h (ng*h/mL)</td>
<td>UR-12788</td>
<td>2.08±0.72</td>
<td>2.64±0.69</td>
<td>3.59±0.49</td>
</tr>
</tbody>
</table>

Comparison of individual AUC0-24h values for Rup, UR-12790 and UR-12788 between Japanese and Caucasians [3]. Caucasians and Japanese PK common time points are 0.01 h, 0.05 h, 0.09 h, 0.13 h, 0.17 h, 0.21 h, 0.25 h, 0.29 h, 0.33 h, 0.37 h, 0.41 h, 0.45 h, 0.49 h, 0.53 h, 0.57 h, 1.00 h, 1.50 h, 2.00 h, 2.50 h, 3.00 h, 3.50 h, 4.00 h, 4.50 h, 5.00 h, 5.50 h, 6.00 h, 6.50 h, 7.00 h, 7.50 h, 8.00 h, 8.50 h, 9.00 h, 9.50 h, 10.00 h, 10.50 h, 11.00 h, 11.50 h, 12.00 h, 12.50 h, 13.00 h, 13.50 h, 14.00 h, 14.50 h, 15.00 h, 15.50 h, 16.00 h, 16.50 h, 17.00 h, 17.50 h, 18.00 h, 18.50 h, 19.00 h, 19.50 h, 20.00 h, 20.50 h, 21.00 h, 21.50 h, 22.00 h, 22.50 h, 23.00 h, 23.50 h, 24.00 h, 24.50 h, 25.00 h, 25.50 h, 26.00 h, 26.50 h, 27.00 h, 27.50 h, 28.00 h, 28.50 h, 29.00 h, 29.50 h, 30.00 h, 30.50 h, 31.00 h, 31.50 h, 32.00 h, 32.50 h, 33.00 h, 33.50 h, 34.00 h, 34.50 h, 35.00 h, 35.50 h, 36.00 h, 36.50 h, 37.00 h, 37.50 h, 38.00 h, 38.50 h, 39.00 h, 39.50 h, 40.00 h, 40.50 h, 41.00 h, 41.50 h, 42.00 h, 42.50 h, 43.00 h, 43.50 h, 44.00 h, 44.50 h, 45.00 h, 45.50 h, 46.00 h, 46.50 h, 47.00 h, 47.50 h, 48.00 h, 48.50 h, 49.00 h, 49.50 h, 50.00 h, 50.50 h, 51.00 h, 51.50 h, 52.00 h, 52.50 h, 53.00 h, 53.50 h, 54.00 h, 54.50 h, 55.00 h, 55.50 h, 56.00 h, 56.50 h, 57.00 h, 57.50 h, 58.00 h, 58.50 h, 59.00 h, 59.50 h, 60.00 h, 60.50 h, 61.00 h, 61.50 h, 62.00 h, 62.50 h, 63.00 h, 63.50 h, 64.00 h, 64.50 h, 65.00 h, 65.50 h, 66.00 h, 66.50 h, 67.00 h, 67.50 h, 68.00 h, 68.50 h, 69.00 h, 69.50 h, 70.00 h, 70.50 h, 71.00 h, 71.50 h, 72.00 h, 72.50 h, 73.00 h, 73.50 h, 74.00 h, 74.50 h, 75.00 h, 75.50 h, 76.00 h, 76.50 h, 77.00 h, 77.50 h, 78.00 h, 78.50 h, 79.00 h, 79.50 h, 80.00 h, 80.50 h, 81.00 h, 81.50 h, 82.00 h, 82.50 h, 83.00 h, 83.50 h, 84.00 h, 84.50 h, 85.00 h, 85.50 h, 86.00 h, 86.50 h, 87.00 h, 87.50 h, 88.00 h, 88.50 h, 89.00 h, 89.50 h, 90.00 h, 90.50 h, 91.00 h, 91.50 h, 92.00 h, 92.50 h, 93.00 h, 93.50 h, 94.00 h, 94.50 h, 95.00 h, 95.50 h, 96.00 h, 96.50 h, 97.00 h, 97.50 h, 98.00 h, 98.50 h, 99.00 h, 99.50 h, 100.00 h.

Conclusions

- No significant differences between Japanese and Caucasians regarding safety, tolerability, PK and cognitive effects were observed:
  1. Dose proportionality analysis supports linearity;
  2. The half-life (t1/2) of Rup is dose dependent ranging from 10 to 40 mg;
  3. Rup is safe and well tolerated in doses ranging from 10 to 40 mg;
  4. Exposure to Rup is similar for Japanese and Caucasians.
- Cognitive effects were assessed to exclude large differences between Japanese and Caucasian subjects:
  1. The therapeutic dose of 10 mg does not appear to affect cognitive function as measured by RVP, SWM, RT1 and VAS;
  2. 20 and 40 mg doses show impairments in RVP (ability to sustain attention) and RT (psychomotor speed), therefore the 10 mg dose is similar to Caucasians.

References

1. Täbel J, Ferber G, Cardas M, Fernandes S, Santamaria E, Izquierdo I. Cognitive function tests at 1 and 3 h after administration of placebo, 10, 20 and 40 mg of Rup on Days 1 and 5.

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