Introduction

- Currently available anticoagulants – which are recommended for a variety of conditions, including the prevention of venous thromboembolism (VTE) after major orthopaedic surgery – often require dose adjustment in older patients, patients with extreme body weight, and for gender.

- Rivaroxaban (BAY 59-7939) is a novel, oral, direct Factor Xa (FXa) inhibitor in advanced clinical development for the prevention and treatment of thromboembolic disorders, including thromboprophylaxis after major orthopaedic surgery.

Objectives

- In order to determine whether fixed dosing of rivaroxaban may be feasible in the clinical setting, the influences of age, gender and weight on the pharmacology and safety of rivaroxaban in healthy subjects were investigated.

Subjects and Methods

Study designs and treatments

- Two randomized, single-blind, placebo-controlled, parallel-group studies were conducted in Caucasian subjects:
  - One study investigated the effects of age and gender on the pharmacology and safety of rivaroxaban in subjects enrolled in four discrete groups: young males or females (aged 18–45 years), and elderly males or females (aged >75 years).
  - The second study investigated the effects of weight on the pharmacology and safety of rivaroxaban in subjects in three weight groups (<50 kg, 50–80 kg [normal] and >120 kg).

- Subjects were randomly assigned to receive a single dose of rivaroxaban 10 mg or placebo.

- Both studies were conducted in accordance with the Declaration of Helsinki and with the approval of the local ethics committees. Subjects provided written, informed consent.

Assessments

- The pharmacokinetic (PK) parameters assessed included rivaroxaban exposure (measured by the area under the concentration-time curve) and maximum rivaroxaban plasma concentrations (C max).

- The pharmacodynamic (PD) effects of rivaroxaban were measured by assessing inhibition of FXa activity and prolongation of prothrombin time (PT).

- An exploratory ANOVA was used to investigate the effects of age, gender and weight on the PK and PD parameters.

- Subjective and objective safety and tolerability were assessed.

Results

Study populations

- A total of 34 healthy subjects were enrolled in the age and gender study (Table 1):
  - A young female withdrew from the study after dosing; therefore, 33 subjects were valid for PK and PD analyses and 34 for safety analysis.

- A total of 48 subjects were enrolled in the weight study (Table 2):
  - The 50 kg group contained females only, because it was not possible to find healthy, adult, Caucasian, male subjects of this weight.

Weight

- Rivaroxaban exposure was not influenced by weight, and there was no relevant difference in the C max of rivaroxaban between the >120 kg group and the normal weight group; however, C max was increased by approximately 24% in the <50 kg weight group compared with normal-weight subjects (Figure 18).

- The increase in C max in subjects weighing >50 kg had no substantial effect on inhibition of FXa activity or prolongation of PT.

Safety and tolerability

- Rivaroxaban was well tolerated by all subjects across both studies; all events were mild to moderate in intensity and resolved without treatment.

Table 1. Demographics of the age and gender study population (n=34)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Young males (n=17)</th>
<th>Young females (n=10)</th>
<th>Elderly males (n=8)</th>
<th>Elderly females (n=10)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>30.3 (18.0–43.0)</td>
<td>33.9 (22.0–43.0)</td>
<td>76.8 (74.0–83.0)</td>
<td>77.8 (75.0–83.0)</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>81.3±13.7</td>
<td>70±6.9</td>
<td>80.1±14.4</td>
<td>67±4.7</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>181.4±8.9</td>
<td>168.7±6.6</td>
<td>171.4±7.2</td>
<td>159.4±4.3</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>24.6±3.3</td>
<td>24.6±2.5</td>
<td>27.2±1.8</td>
<td>26.6±3.0</td>
</tr>
<tr>
<td>Creatinine clearance (ml/min)</td>
<td>120.0±9.3</td>
<td>121.0±20.1</td>
<td>59.1±6.0</td>
<td>51.8±18.4</td>
</tr>
</tbody>
</table>

*Mean (range); #mean ± standard deviation; *six subjects received rivaroxaban, the remainder received placebo.

Conclusions

- Rivaroxaban exposure and the AUaE for PD effects were slightly higher in elderly compared with young subjects. This was thought to be partially due to delayed renal clearance of rivaroxaban caused by decreased renal function, a well-accepted consequence of advancing age.

- Gender had no significant effect on the PK or PD of rivaroxaban.

- Weight had only a small influence on the PK and PD of rivaroxaban; the small increase in the C max of rivaroxaban observed in subjects with low body weight (~24%) was not thought to be clinically relevant.

- Rivaroxaban was well tolerated in all subjects, regardless of age, gender or weight.

- Overall, these results suggest that rivaroxaban may be administered at a fixed dose, irrespective of age, gender or weight.

- Phase II studies of rivaroxaban for the prevention of VTE after major orthopaedic surgery support this conclusion; in these studies, fixed doses of rivaroxaban were administered to male and female patients aged 26–93 years, weighing between 45 and 173 kg.

- Confirmation of these findings may be provided by the ongoing phase III programme in this indication, in which rivaroxaban will be administered in fixed doses irrespective of age, gender or body weight.

References