Introduction

Anticoagulants are the cornerstone of prevention and treatment of thrombotic disorders. One of the key clinical uses is limited by a dose-dependent risk of bleeding.1 2 Data from a phase 2 proof-of-concept study demonstrate that suppression of Factor XI (FXI) levels reduces the risk of VTE and is associated with a numerically lower rate of bleeding events than treatment with warfarin in patients undergoing long-term replacement.3 4 Inhibition of FXa, therefore offers the potential to reduce the risk of thrombosis while minimizing the risk of anticoagulation-associated bleeding and an attractive target mechanism for novel antithrombotic therapies.

BAY 12/13790 fully blocks the coagulation cascade and inhibits the catalytic domain of FXa, resulting in inhibition of the intrinsic activation and amplification loop of the coagulation cascade.

Objectives

To evaluate the safety, pharmacokinetic (PK) and pharmacodynamic (PD) properties of BAY 12/13790, a fully human IgG1 antibody targeting FXa, in healthy male volunteers.

Methods

Volunteers

Healthy Caucasian male volunteers aged 18–55 years with a body mass index in the range 18–30 kg/m2 were eligible for inclusion in this study. Key exclusion criteria were: known coagulation disorders or conditions that increases bleeding risk; known severe allergies or hypersensitivity to the study drug or any of its components; use of medications that may have an impact on the study objectives; the presence of relevant diseases in the 4 weeks preceding the study; and a history of heavy smoking or drug or alcohol abuse.

The study was conducted in accordance with the ethical principles of the Declaration of Helsinki and in compliance with the International Conference on Harmonisation guidelines for Good Clinical Practice. The protocol was approved by the local ethics committee and all volunteers provided written informed consent.

Study design

This was a phase 1, single-center, randomized, single-blind, parallel-group, placebo-controlled dose-exploration study (Figure 1). Eligible volunteers were randomized in a 4:1 ratio to receive a single dose of BAY 12/13790 or placebo (isotonic sodium chloride solution, 0.9%) as a 60-minute intravenous infusion.

Nine volunteers (0.06, 0.15, 0.30, 0.60, 2.50, 5.00 or 10.00 mg/kg of BAY 12/13790) were studied (Figure 1), with a planned sample size of 10 volunteers per dose cohort (eight receiving BAY 12/13790 and two receiving placebo) to allow for exclusion of volunteers if safety and tolerability were unacceptable with the preceding dose.

Results

Demographics and disposition

In total, 83 volunteers were randomized to receive BAY 12/13790 or placebo (Figure 1; patient demographics are shown in Table 1). Valid safety, PK and PD measurements were obtained from a total of 81, 80 and 80 volunteers, respectively (Figure 1).

Safety

No cases of spontaneous or prolonged bleeding or thrombocytopenia were observed. No relevant anti-drug antibody formation was observed over the study period. No relevant anti-drug antibody formation was observed over the study period.

Pharmacokinetics

BAY 12/13790 was measured using validated enzymelinked immunosorbent assay. PK parameters were calculated using the model-independent (compartments free) method and the non-linear mixed-effects software program of Modelix™ (Certara, Princeton, NJ, USA) and included AUUC0–t (area under the plasma concentration-time curve from time 0 to T divided by dose and maximum observed plasma concentration [Cmax]).

Pharmacodynamics

The PD properties of BAY 12/13790 that were evaluated included: activated partial thromboplastin time (aPTT); clotting time; and coagulation factor assays.

Conclusions

Overall, BAY 12/13790 demonstrated a favorable safety and tolerability profile with no cases of bleeding or hyperfibrinolysis and low potential for immunogenicity following administration in healthy volunteers. Administration of BAY 12/13790 resulted in dose-dependent increases in exposure, aPTT and clotting time.

Pharmacodynamics

Following administration of BAY 12/13790, there was a dose-dependent increase in aPTT and clotting time (Figure 4).

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Table 1. Demographics.

<table>
<thead>
<tr>
<th>Age (years), Mean (SD)</th>
<th>Weight (kg), Mean (SD)</th>
<th>BMI, Mean (SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>39.3 (6.4)</td>
<td>81.3 (14.0)</td>
<td>26.3 (4.2)</td>
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Table 2. Pharmacodynamic parameters.

<table>
<thead>
<tr>
<th>BAY 12/13790</th>
<th>Placebo</th>
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<tbody>
<tr>
<td>0.06 mg/kg</td>
<td>0.15 mg/kg</td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>0.06 mg/kg</td>
</tr>
<tr>
<td>Tmax (h)</td>
<td>0.06 mg/kg</td>
</tr>
<tr>
<td>Cmax (ng/mL)</td>
<td>0.06 mg/kg</td>
</tr>
</tbody>
</table>

References


Figure 1. Plasma concentration-time profile of total BAY 12/13790 in healthy volunteers up to 150 h after dosing.

Figure 2. Effects of increasing doses of BAY 12/13790 on aPTT in healthy volunteers up to 7 days after dosing.

Figure 3. Effect of increasing doses of BAY 12/13790 on clotting time measured by rotational thromboelastometry for up to 7 days after dosing.

Figure 4. Effect of increasing doses of BAY 12/13790 on bleeding time measured using the Surgicell™ system.