Aetiology and treatment of venous thromboembolism
Bank, I.

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A Novel Long-acting Synthetic Factor Xa Inhibitor (SanOrg 34006) to Replace Warfarin for Secondary Prevention in Deep Venous Thrombosis. A Phase II Evaluation

The PERSIST investigators

1 See appendix

Journal of Thrombosis and Haemostasis 2003 (accepted for publication)
Abstract

Vitamin K antagonists for secondary prevention in patients with deep venous thrombosis require monitoring and dose-adjustments. The synthetic factor Xa inhibitor, SanOrg34006, has predictable pharmacokinetics and may be administered once weekly without dose adjustments.

After 5 to 7 days of enoxaparin treatment, patients with proximal deep venous thrombosis were randomised to receive 2.5, 5.0, 7.5 or 10 mg of SanOrg34006 subcutaneously once weekly or warfarin (INR, 2.0 to 3.0) for 12 weeks. The primary efficacy outcome was the composite of change in thrombotic burden, as assessed by ultrasonography and perfusion lung scanning at baseline and week 12±1, and clinical thromboembolic events. This outcome was classified as normalisation, no relevant change or deterioration. Other outcomes were major and other clinically relevant bleeding.

A total of 659 patients were randomised and treated. In 614 patients (93 percent) the primary efficacy outcome was evaluable. The rates of normalisation and deterioration were similar in all SanOrg34006 groups (p=0.4) and did not differ from the warfarin group. There was a clear dose response for major bleeding among patients treated with SanOrg34006 (p=0.003). Patients receiving 2.5 mg SanOrg34006 had less bleeding than warfarin recipients did (p=0.03).

SanOrg34006 dosed at 2.5 mg appears as effective as higher dosages and warfarin for the secondary prevention in deep venous thrombosis and was not associated with major bleeding. Therefore, 2.5 mg of SanOrg34006 administered subcutaneously once weekly might be a suitable alternative to dose-adjusted oral vitamin K antagonist.
**Introduction**

The initial treatment of patients with venous thromboembolism has recently undergone major changes. In-hospital intravenous unfractionated heparin requiring laboratory monitoring has been largely replaced by body weight adjusted subcutaneous low-molecular-weight heparin \(^1\). This improvement has allowed out of hospital treatment in the majority of patients \(^2\). However, anticoagulation for secondary prevention with vitamin K antagonists such as warfarin remains problematic \(^3\). They have a narrow therapeutic range and are subject to food and drug interactions necessitating frequent monitoring \(^5\). Despite monitoring and dose adjustments, anticoagulant intensity is often outside the target range and associated with bleeding complications and recurrences \(^6\).

Synthetic pentasaccharides are a new class of antithrombotics with specific anti-Xa activity \(^8\). One of these, fondaparinux (half-life 15 hours), was recently found to be effective and safe when administered once daily for the prevention of venous thromboembolism after orthopaedic surgery \(^9\). Another pentasaccharide, SanOrg34006, has a half-life of approximately 4 days, making it suitable for once a week subcutaneous injection. It has linear pharmacokinetics, low inter- and intra-individual variability and may not require monitoring of anticoagulant intensity \(^10\). Therefore, SanOrg34006 might be an alternative to vitamin K antagonists in secondary prevention of venous thromboembolism. Hence, a dose-finding study was conducted in patients with deep venous thrombosis comparing the efficacy and safety of 4 different dosages of SanOrg34006 with warfarin.

**Methods**

**Patients**

Consecutive patients between 18 and 85 years of age with acute symptomatic proximal deep venous thrombosis confirmed by compression ultrasonography or venography were potentially eligible for the study. Exclusion criteria included symptoms for more than 14 days; symptomatic pulmonary embolism; documented deep venous thrombosis within the last two years; surgery within the past 10 days; more than 32 hours of therapeutic anticoagulant treatment; contraindications for anticoagulants; life expectancy less than 3 months; pregnancy; serum creatinine over 200 μmol/L; and a platelet count less than 100x10⁶/L. There was no body weight restriction for eligibility. Participating patients provided written informed consent.
Study Design

Patients received 1 mg/kg enoxaparin subcutaneously twice daily for 5 to 7 days and then underwent a baseline assessment of thrombotic burden by compression ultrasonography of both legs and perfusion lung scanning. Hereafter, randomisation to one of four SanOrg34006 dosages or warfarin took place, stratified for centre and active cancer (defined as not cured or treated within the last 6 months) using a central service. Treatment was blinded for dose of SanOrg34006, but open for type of drug and was continued for 12 weeks. Patients were asked to report any symptoms of recurrent venous thromboembolism or bleeding. At week 12±1 ultrasonography and perfusion lung scanning were repeated to assess change in thrombotic burden. Biochemistry was tested at baseline and at week 12. Initially, samples for platelet counts and trough drug concentrations were collected weekly. SanOrg34006 concentrations were also measured 3 times during 48 hours after administration of the drug in weeks 1, 7 and 12. Later, testing was reduced. The paired baseline and 12 week ultrasonographies and lung scanning results were reviewed by a central adjudication committee, blinded for treatment allocation. This committee also reviewed all suspected episodes of recurrent thrombosis or pulmonary embolism, bleeding and deaths. Safety data were reviewed regularly by the data and safety monitoring committee, partly blinded to SanOrg34006 treatment groups coded as A, B, C, D. Discontinuation of a study arm was to be considered when the difference in the incidence of major bleeding or recurrent symptomatic venous thromboembolism between the warfarin group and any SanOrg34006 group was with 95 percent confidence above zero. The study was conducted in accordance with the declaration of Helsinki and Good Clinical Practice guidelines. The local Institutional Review Boards approved the study.

Treatment Regimens

Patients in the SanOrg34006 groups received any of 4 dosages (2.5, 5.0, 7.5 or 10.0 mg) once weekly, without body weight adjustment (Organon Inc., West-Orange, USA) with the first dose given 6 to 18 hours after the last enoxaparin dosage. The selection of the lowest dosage of 2.5 mg, was based on the consideration that only dosages could be tested in the setting of deep venous thrombosis that are expected to be clinically active. In healthy volunteers this dosage had provided SanOrg34006 concentrations for the period of almost one week that prevented thrombus formation in pre-clinical models. The highest dosage of 10 mg was selected since in healthy volunteers, higher dosages showed
a tendency to puncture site hemorrhages. SanOrg34006, in syringes in 0.5 mL of saline, was given subcutaneously by trained staff or rarely by self-injection. Warfarin was provided and prothrombin time monitoring was performed several times during the first week and at least in weeks 2, 4 and 7. The target International Normalised Ratio (INR) range was 2.0 to 3.0. Patients randomised to warfarin continued with enoxaparin until the INR was above 2.0 for more than 48 hours. During randomised treatment concomitant use of other anticoagulants, clopidogrel and glycoprotein IIb/IIIa antagonist was prohibited, and use of aspirin and non-steroidal anti-inflammatory drugs was discouraged. After 12 weeks further treatment was left at the discretion of the investigator.

Efficacy Outcomes
Bilateral compression ultrasonography was performed at standardised sites at the inguinal ligament (common femoral vein), mid-thigh (superficial femoral vein) and popliteal fossa (popliteal vein) and the diameter at compression was recorded. Normalisation of ultrasonography at week 12 was defined as a diameter of less than or equal to 2 mm at each of the 6 sites. Deterioration was defined as an increase in diameter of more than 2 mm or more than 25% at any site. Other results were classified as no relevant change.

Perfusion lung scanning was performed after the intravenous injection of 70 to 100 MBq $^{99m}$Tc-Technetium labelled macro-aggregates of albumin. Imaging was performed in six views and the remaining perfusion in the 6 lobes was scored. Normalisation was defined as a normal perfusion of all lobes at week 12 and deterioration as reduction of at least 25 percent of perfusion in any lobe. Other results were classified as no relevant change.

Symptomatic recurrent venous thromboembolism was considered present when confirmed by objective tests. All deaths were reviewed to assess the likelihood of pulmonary embolism or bleeding as the cause of death. Sudden death where pulmonary embolism could not be excluded was classified as unexplained death. The primary efficacy outcome was the change in thrombotic burden between baseline and week 12, and classified as deterioration, no relevant change or normalisation. Deterioration was defined as the composite of fatal and non-fatal recurrent venous thromboembolism, unexplained death, and asymptomatic worsening of the ultrasonography or lung scan. Normalisation was defined as the combination of a normalised ultrasonography and lung scan. Other combinations were classified as no relevant change.
Safety Outcomes

The primary safety outcome was major bleeding, defined as clinically overt bleeding that was fatal, retroperitoneal, intracranial, within a critical organ, leading to a decrease in hemoglobin of more than 2 g/dL, or required a transfusion of 2 units or more of packed cells. Bleeding episodes, that were considered clinically relevant but not qualifying for major, were a secondary safety outcome (e.g., epistaxis that required interventions or lasted more than 5 minutes and spontaneous hematuria). Bleeds were counted during 13 weeks after randomisation. Additional safety outcomes considered were thrombocytopenia (platelet count below 100×10^9/L, or a drop of more than 40 percent) associated with anti-platelet antibodies, adverse events and mortality.

Laboratory Analysis

Plasma concentrations of SanOrg34006 (mg/L) were centrally determined by an inhibition assay. Residual factor Xa activity was measured with a chromogenic substrate in diluted plasma samples after addition of known quantities of factor Xa and an excess of antithrombin. Areas under the curve were calculated for the dosage interval of 168 hours.

Statistical Analysis

Efficacy analyses were performed in all randomised patients who received treatment, for whom DVT at baseline was confirmed, and for whom the primary efficacy outcome was evaluable. Trends among the SanOrg34006 dose groups with respect to the change in thrombotic burden were assessed using the Cochran-Mantel-Haenszel test based on rank scores, stratified by active cancer as well as pairwise comparisons between each SanOrg34006 dose group and warfarin. The impact of baseline covariates on the dichotomised outcome (deterioration versus no deterioration) was described by calculating (unadjusted) odds ratios and 95% confidence intervals.

Safety analyses were performed in all randomised patients who received treatment. Trends among the SanOrg34006 dose groups in the incidence of major and other clinically relevant bleeding were assessed based on the Cochran-Armitage test. Pairwise differences between the SanOrg34006 dose groups and the warfarin group were assessed similarly. The sample size of 100 patients per group would provide 80 percent power (2-sided type I error of 5 percent) to detect differences of 20 percent in incidences of deterioration between the more effective group and the less effective SanOrg34006 group. To allow for missing outcome data the sample size was set at 130 patients per group.
Results

Study Population

From August 1999 to April 2001, 701 patients were enrolled. Out of these, 40 patients, who received initial enoxaparin therapy were not randomised due to hemorrhage (n=6), other adverse events (n=5), suspected (n=5) or verified (n=2) recurrence of venous thromboembolism or other reasons (n=22) such as withdrawal of consent. An additional 2 patients withdrew consent after randomisation prior to receiving randomised treatment. The baseline characteristics of the 659 patients who received randomised treatment are shown in Table 1. The groups were comparable regarding these characteristics. In 614 patients (93 percent) the primary efficacy outcome was available for analysis.

Table 1 Baseline characteristics and treatment details of all patients who received randomised treatment.

<table>
<thead>
<tr>
<th>Outcome</th>
<th>2.5 mg (N=131)</th>
<th>5 mg (N=135)</th>
<th>7.5 mg (N=130)</th>
<th>10 mg (N=131)</th>
<th>Warfarin (N=132)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age, years, mean (S.D.)</strong></td>
<td>58.1 (17.2)</td>
<td>59.5 (16.3)</td>
<td>60.0 (13.5)</td>
<td>59.1 (14.7)</td>
<td>60.0 (14.8)</td>
</tr>
<tr>
<td><strong>Male sex, n (%)</strong></td>
<td>69 (42.7)</td>
<td>73 (54.1)</td>
<td>83 (63.0)</td>
<td>63 (49.0)</td>
<td>71 (53.8)</td>
</tr>
<tr>
<td><strong>Body weight, kg, mean (S.D.)</strong></td>
<td>81.4 (15.8)</td>
<td>78.7 (15.2)</td>
<td>82.3 (14.8)</td>
<td>78.7 (14.9)</td>
<td>77.9 (15.3)</td>
</tr>
<tr>
<td><strong>History of VTE, n (%)</strong></td>
<td>28 (21.1)</td>
<td>25 (18.5)</td>
<td>31 (23.8)</td>
<td>27 (20.6)</td>
<td>25 (18.9)</td>
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<tr>
<td><strong>Documented active cancer, n (%)</strong></td>
<td>10 (7.6)</td>
<td>13 (9.6)</td>
<td>7 (5.4)</td>
<td>11 (8.4)</td>
<td>10 (7.6)</td>
</tr>
<tr>
<td><strong>Enoxaparin treatment pre-randomisation, duration in days, mean (S.D.)</strong></td>
<td>6.1 (0.9)</td>
<td>6.1 (0.9)</td>
<td>5.9 (0.8)</td>
<td>6.0 (0.9)</td>
<td>6.0 (0.9)</td>
</tr>
<tr>
<td><strong>Enoxaparin treatment post-randomisation, duration in days, mean (S.D.)</strong></td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>7.7 (1.8)</td>
</tr>
<tr>
<td><strong>Number of S.C. SanOrg34006 administrations, mean (S.D.)</strong></td>
<td>11.5 (2.0)</td>
<td>11.4 (1.9)</td>
<td>11.6 (1.6)</td>
<td>10.9 (2.7)</td>
<td>-</td>
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<td><strong>Thrombotic burden at baseline:</strong></td>
<td></td>
<td></td>
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<td></td>
<td></td>
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<tr>
<td>Two or more locations of non-compressibility</td>
<td>68 (52.3)</td>
<td>71 (53.1)</td>
<td>71 (54.6)</td>
<td>70 (53.9)</td>
<td>73 (56.6)</td>
</tr>
<tr>
<td>Perfusion defect present, n (%)*</td>
<td>70 (53.1)</td>
<td>65 (49.9)</td>
<td>84 (63.6)</td>
<td>66 (50.8)</td>
<td>71 (56.1)</td>
</tr>
<tr>
<td><strong>Area under the time-concentration curve, mg*h/L, mean (S.D.):</strong></td>
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<tr>
<td>Week 1</td>
<td>16.1 (15.3)</td>
<td>88.1 (21.7)</td>
<td>130 (28.2)</td>
<td>17.3 (11.1)</td>
<td>-</td>
</tr>
<tr>
<td>Week 7</td>
<td>81.6 (19.3)</td>
<td>160 (15.1)</td>
<td>230 (63.5)</td>
<td>290 (71.3)</td>
<td>-</td>
</tr>
<tr>
<td>Week 12</td>
<td>80.4 (21.2)</td>
<td>176 (14.7)</td>
<td>285 (59.4)</td>
<td>363 (92.8)</td>
<td>-</td>
</tr>
<tr>
<td>Premature discontinuations and reasons:</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Total number</td>
<td>8</td>
<td>15</td>
<td>7</td>
<td>28</td>
<td>8</td>
</tr>
<tr>
<td>Bleeding complication, n (%)</td>
<td>0</td>
<td>5 (3.7)</td>
<td>2 (1.5)</td>
<td>10 (7.6)</td>
<td>2 (1.5)</td>
</tr>
<tr>
<td>Recurrent DVT PE, n (%)</td>
<td>2 (1.5)</td>
<td>1 (0.7)</td>
<td>0</td>
<td>1 (0.8)</td>
<td>1 (0.8)</td>
</tr>
<tr>
<td>Death, n (%)</td>
<td>1 (0.8)</td>
<td>5 (3.7)</td>
<td>0</td>
<td>1 (0.8)</td>
<td>0</td>
</tr>
<tr>
<td>Other adverse event, n (%)</td>
<td>3 (2.3)</td>
<td>8 (4.9)</td>
<td>6 (4.2)</td>
<td>10 (7.6)</td>
<td>3 (2.3)</td>
</tr>
<tr>
<td>Comorbid condition and other reasons</td>
<td>2 (1.5)</td>
<td>1 (0.7)</td>
<td>1 (0.8)</td>
<td>7 (5.3)</td>
<td>2 (1.5)</td>
</tr>
</tbody>
</table>
Treatment and Follow-up
Details on the initial and long-term treatment are shown in Table 1. In the SanOrg34006 groups compliance was high with 95 percent of injections given. Pharmacokinetic parameters had a linear relationship to the dose, and there was an accumulation of the drug concentrations in all groups during the study period. Steady state was reached at week 12. Among the warfarin-treated patients an average of 14 determinations of the Prothrombin time were performed, and 35, 51 and 15 percent were below, within and above the therapeutic range, respectively. There were 66 premature discontinuations of treatment with study drug (Table 1).

Efficacy Outcomes
The overall change in thrombotic burden in the treatment groups is shown in Table 2. The rates of normalisation and deterioration were similar in all groups. The test for trend among the SanOrg34006 dosage groups did not show significant differences (P=0.9). The rate of symptomatic recurrent venous thromboembolism was low and no patient experienced fatal pulmonary embolism. Additional analyses showed that 7 out of 40 evaluable patients with active cancer had deterioration (18 percent) versus 39 of 574 patients (7 percent) without active cancer (odds ratio 2.9; 95 percent confidence interval 1.2-7.0). Similarly, 16 out of 129 evaluable patients with a history of previous venous thromboembolism (12 percent) had a deterioration versus 30 of 485 patients (6 percent) without such a history (odds ratio 2.2; 95 percent confidence interval 1.1-4.1). Gender, age, creatinine clearance, body weight and pharmacokinetic parameters were not associated with differences in frequency of deterioration.

Safety Outcomes
The incidence of bleeding episodes and deaths is shown in Table 2. Two patients, both in the 5-mg SanOrg34006 group, had a fatal hemorrhage (intracranial and gastro-intestinal) during the study period. Among patients treated with SanOrg34006 there was a statistically significant dose response relationship for major bleeds (P=0.003) and for major and other clinically relevant bleeds (P=0.001). The incidence of major hemorrhages in the 10-mg SanOrg34006 group was statistically significantly higher than in the warfarin group (P=0.010). After the second interim analysis and during the 3 month treatment period a pattern with a high incidence of bleeding episodes combined with unusual types of bleeding emerged, and it was subsequently decided to stop further treatment
Table 2 Efficacy and safety outcomes in all patients who received randomised treatment.

<table>
<thead>
<tr>
<th>Outcome</th>
<th>2.5 mg (N=131)</th>
<th>SanOrg34006 5 mg (N=133)</th>
<th>7.5 mg (N=130)</th>
<th>10 mg (N=131)</th>
<th>Warfarin (N=132)</th>
</tr>
</thead>
</table>

**Changes in thrombotic burden:**
- No efficacy outcome assessment available, n (95% confidence interval)
- Normalisation, n (%*)
  - 2.5 mg: 32 (25.6)
  - 5 mg: 31 (24.2)
  - 7.5 mg: 29 (21.6)
  - 10 mg: 30 (25.2)
  - Warfarin: 31 (25.9)
- No relevant change, n (%*)
  - 2.5 mg: 87 (69.6)
  - 5 mg: 89 (69.5)
  - 7.5 mg: 81 (68.6)
  - 10 mg: 71 (62.2)
  - Warfarin: 84 (67.7)
- Deterioration, n (%*)
  - 2.5 mg: 6 (1.8)
  - 5 mg: 8 (6.3)
  - 7.5 mg: 8 (6.8)
  - 10 mg: 15 (12.6)
  - Warfarin: 9 (7.3)

**Components of deterioration:**
- Compression ultrasound, n (%*)
  - 2.5 mg: 6 (1.6)
  - 5 mg: 8 (6.3)
  - 7.5 mg: 8 (6.8)
  - 10 mg: 1.8 (1.6)
  - Warfarin: 2.7 (1.6)
- Perfusion lung scan, n (%*)
  - 2.5 mg: 1 (3.2)
  - 5 mg: 1 (3.2)
  - 7.5 mg: 2 (3.2)
  - 10 mg: 1 (3.2)
  - Warfarin: 2 (3.2)
- Symptomatic DVT, n (%*)
  - 2.5 mg: 0
  - 5 mg: 0
  - 7.5 mg: 0
  - 10 mg: 0
  - Warfarin: 0
- Symptomatic PE, n (%*)
  - 2.5 mg: 0
  - 5 mg: 0
  - 7.5 mg: 0
  - 10 mg: 2 (1.6)
  - Warfarin: 0
- Symptomatic DVT+PE, n (%*)
  - 2.5 mg: 0
  - 5 mg: 0
  - 7.5 mg: 0
  - 10 mg: 0
  - Warfarin: 0
- Unexplained death, n (%*)
  - 2.5 mg: 0
  - 5 mg: 0
  - 7.5 mg: 0
  - 10 mg: 0
  - Warfarin: 0

**Hemorrhage, major and all:**
- Major hemorrhage, n (%)
  - 2.5 mg: 0 (0.0%)
  - 5 mg: 0 (0.0%)
  - 7.5 mg: 2 (1.5%)
  - 10 mg: 9 (6.9%)
  - Warfarin: 1 (0.8%)
- 95% confidence interval
  - 2.5 mg: (0.0-2.8)
  - 5 mg: (0.0-2.8)
  - 7.5 mg: (1.2-3.4)
  - 10 mg: (3.2-12.6)
  - Warfarin: (0.0-4.1)
- p-value compared to warfarin
  - 2.5 mg: NS
  - 5 mg: NS
  - 7.5 mg: NS
  - 10 mg: 0.040
  - Warfarin: 0.040
- All hemorrhage *, n (%)
  - 2.5 mg: 3 (2.3%)
  - 5 mg: 16 (11.9%)
  - 7.5 mg: 18 (13.8%)
  - 10 mg: 20 (15.3%)
  - Warfarin: 11 (8.3%)
- 95% confidence interval
  - 2.5 mg: (0.5-6.6)
  - 5 mg: (4.9-8.5)
  - 7.5 mg: (8.1-21.0)
  - 10 mg: (9.6-22.6)
  - Warfarin: (1.2-14.1)
- p-value compared to warfarin
  - 2.5 mg: 0.029
  - 5 mg: 0.029
  - 7.5 mg: 0.081
  - 10 mg: 0.081
  - Warfarin: 0.081

**Deaths:**
- n (%)
  - 2.5 mg: 1 (0.8%)
  - 5 mg: 1 (0.8%)
  - 7.5 mg: 0
  - 10 mg: 1 (0.8%)
  - Warfarin: 0
- Causes of Death:
  - Major bleeding
    - 2.5 mg: 0
    - 5 mg: 2 (1.5%)
    - 7.5 mg: 0
    - 10 mg: 0
    - Warfarin: 0
  - Other known cause
    - 2.5 mg: 1 (0.8%)
    - 5 mg: 1 (0.8%)
    - 7.5 mg: 0
    - 10 mg: 1 (0.8%)
    - Warfarin: 0
  - Cause unknown
    - 2.5 mg: 0
    - 5 mg: 2 (1.5%)
    - 7.5 mg: 0
    - 10 mg: 0
    - Warfarin: 0

* Relative to the number of evaluable patients  
* Major + other clinically relevant hemorrhages

in those in the 10-mg group, based on advice from the safety committee. The incidence of any bleeding complication was lower in the 2.5-mg SanOrg34006 group compared to the warfarin group (P=0.029). The occurrence of bleeding in relation to time in the study is depicted in Figure 1. Other adverse events were distributed similarly between the groups. During the enoxaparin treatment there was an increase to above 3 times the upper limit of normal of alanine aminotransferase in 97 patients (15 percent). At week 12 alanine aminotransferase was elevated in 4 patients (0.8 percent) on SanOrg34006 and in none on warfarin. Heparin-induced immune thrombocytopenia was not observed in patients treated with SanOrg34006 or warfarin.
<table>
<thead>
<tr>
<th>Week</th>
<th>1</th>
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<th>5</th>
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<tr>
<td>warfarin</td>
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<td>2.5 mg SanOrg34006</td>
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**Discussion**

This dose-finding study, evaluating four fixed dosages of SanOrg34006, suggests that this compound in its lowest dose tested might be a suitable alternative to monitored vitamin K antagonists in the secondary prevention of recurrences in patients with deep venous thrombosis. SanOrg34006 is a long-acting selective anti-Xa-inhibitor, which is administered subcutaneously once weekly and does not require dose adjustments. The range of dosages was selected on the basis of the results from phase I studies, evaluating trough levels, coagulation parameters and bleeding in order to protect the patients against the consequences of undertreating thrombosis or overdosing with an anticoagulant.

The study was designed to explore SanOrg34006 for secondary prevention and thus initial treatment was standardised, using a low-molecular-weight heparin for 5-7 days before randomisation. The extended mean 8 days treatment with low-molecular-weight heparin in the warfarin group, necessary for INR stabilisation, is unlikely to have had an impact on the efficacy outcome, in view of previous studies demonstrating equal effects of immediate and delayed introduction of vitamin K antagonist therapy. No statistically significant differences in primary efficacy outcome were seen between the dose-groups. How should this flat dose-response be interpreted? The observed low incidence of symptomatic recurrences of 1.0 percent in 490 SanOrg34006-treated patients was similar to that of the warfarin group (1.6 percent). The observed low incidence may be partly explained...
by the low number of patients with active cancer (8 percent). Nevertheless, our results derived from a large number of patients indicate that we are likely to be on the upper plateau of the dose-response curve. The statistically non-significant increased role of deterioration of thrombotic burden in the 10 mg group is not due to a different risk profile of these patients and is therefore difficult to explain. The diagnostic strategy featuring a combination of symptomatic recurrent events and asymptomatic changes on repeat compression ultrasonography and perfusion lung scanning has previously shown clinical validity for the assessment of the initial therapy and to be predictive for later clinical outcome. In the current study this strategy was used to assess the 3-month period of secondary prevention. Although we did not observe an association between the dosages and the change in thrombotic burden, an association with risk factors, such as active cancer or previous thromboembolism, was seen. Furthermore, this strategy is in line with the policies of regulatory agencies, which recommend using a composite endpoint, consisting of all clinical thromboembolic events and subclinical signs of progression detected by routine screening.

At variance with the efficacy analysis, the safety analysis showed a clear dose-response with an unacceptably high frequency of major bleeding in the SanOrg34006 10-mg group (leading to a premature discontinuation in this group of those already randomised) and none in the 2.5-mg group. Also the rate of other clinically relevant haemorrhages was low in the 2.5-mg group, but increased in the higher dosage groups. The 0.8 percent frequency of major bleeding in the warfarin group is consistent with the range of 0.9-2.2 percent reported in the literature. SanOrg34006 does not have a specific antidote, however, the pharmacological effects could potentially be antagonised by procoagulant drugs including prothrombin complex concentrate and in case of severe bleeding recombinant activated factor VII.

After consideration of all the available data in this dose-finding study, a SanOrg34006 dosage of 2.5 mg seems optimal. This dosage appeared as effective as the higher dosages and warfarin. No major bleeding and a low frequency of other clinically relevant bleedings, which are likely to impact the quality of life, were observed with this dose. In fact, the lowest dosage of SanOrg34006 was associated with fewer bleeding complications than warfarin. Although lower dosages than 2.5 mg were not studied in the present setting, they could be associated with lower efficacy, whereas further improvement in safety is unlikely. The combination of an effective and safe drug, that does not require monitoring and dose adjustments, makes SanOrg34006 at a dosage of 2.5 mg an attractive
anticoagulant to replace vitamin K antagonists. The convenient regimen of once-weekly administration should improve compliance compared with both vitamin K antagonists and other therapies such as low-molecular-weight heparin injected subcutaneously every day. Another advantage is the absence of heparin-induced immune thrombocytopenia. Pharmacokinetic analyses showed that accumulation of SanOrg34006 occurred that approached steady state towards the end of the treatment period.

Some limitations of our study require comment. This was a partially open trial. However, to minimise the potential for bias, randomisation was centralised and adjudication of outcome events was blinded. The ultrasonographs and lung scans were read pairwise, which may favour the observation of improvement. However, this applies to all groups. Finally, the acceptance by patients of weekly subcutaneous injections could not be assessed in the setting of this study. It remains to be established whether patients prefer weekly injections or oral medication with repeated blood sampling.

Further studies comparing 2.5 mg of SanOrg34006 with warfarin, using clinical outcomes, are warranted in patients with venous thromboembolism for treatment and secondary prevention. SanOrg34006 may also be a valuable anticoagulant for other indications, including extended postoperative prophylaxis, atrial fibrillation and in acute coronary syndromes.

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References


Appendix


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