

Oral, Direct Factor Xa Inhibition with BAY 59-7939 for the Prevention of Venous Thromboembolism After Total Hip Replacement

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INTRODUCTION

Background: Joint replacement surgery is an appropriate model for dose-ranging studies investigating new anticoagulants.

Objective: To assess the efficacy and safety of a novel, oral, direct factor Xa (FXa) inhibitor—BAY 59-7939—relative to enoxaparin in patients undergoing elective total hip replacement.

METHODS

In this double-blind, double-dummy, dose-ranging study, patients were randomized to oral BAY 59-7939 (2.5, 5, 10, 20, or 30 mg b.i.d.), starting 6-8 h after surgery, or s.c. enoxaparin 40 mg once daily, starting on the evening before surgery. Treatment was continued until mandatory bilateral venography was performed 5-9 days after surgery.

RESULTS

Of 706 patients treated, 548 were eligible for the primary efficacy analysis. The primary efficacy endpoint was the incidence of any deep vein thrombosis, non-fatal pulmonary embolism, and all-cause mortality; rates were 15%, 14%, 12%, 18%, and 7% for BAY 59-7939 2.5, 5, 10, 20, and 30 mg b.i.d., respectively, compared with 17% for enoxaparin. The primary efficacy analysis did not demonstrate any significant trend in dose-response relationship for BAY 59-7939. The primary safety endpoint was major, postoperative bleeding; there was a significant increase in the frequency of events with increasing doses of BAY 59-7939 ($P=0.045$), but no significant differences between individual BAY 59-7939 doses and enoxaparin.

CONCLUSION

When efficacy and safety were considered together, the oral, direct FXa inhibitor BAY 59-7939, at 2.5-10 mg b.i.d., compared favorably with enoxaparin for the prevention of venous thromboembolism in patients undergoing elective total hip replacement. In summary, in patients at high risk of developing thrombosis and bleeding, direct FXa inhibition with BAY 59-7939 was effective across the dose range studied, and compared favorably with enoxaparin; safety was similar between BAY 59-7939 2.5–10 mg b.i.d. and enoxaparin. These results warrant further evaluation of BAY 59-7939 for use as an antithrombotic agent in patients in whom the risk of developing thrombosis persists.

RESULTS (CONT.)

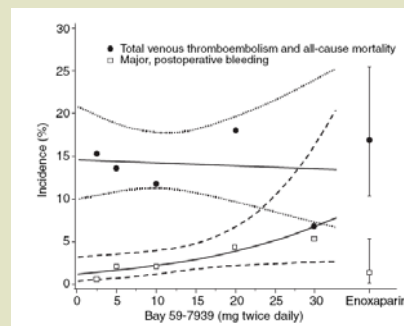


Figure 1. Dose–response relationship between BAY 59-7939 and the primary efficacy endpoint (DVT, non-fatal PE, all-cause mortality; per-protocol population) and the primary safety endpoint (major, postoperative bleeding events; safety population). The solid lines are the dose-response curves for BAY 59-7939, estimated by logistic regression, including total daily dose as a covariate. The dotted lines represent the 95% confidence intervals for the primary efficacy endpoint, and the dashed lines the 95% confidence intervals for the primary safety endpoint.

Table 2. Incidence of major, postoperative bleeding and its components, secondary bleeding-related endpoints, and site of the bleeding event, as assessed by a central, blinded adjudication committee ($n = 704$; safety population)

Bleeding classification	BAY 59-7939 b.i.d.					Enoxaparin (once daily)
	2.5 mg (n = 132)	5 mg (n = 136)	10 mg (n = 133)	20 mg (n = 134)	30 mg (n = 37)*	40 mg (n = 132)
Major, postoperative bleeding, n (%)†	1 (0.8)	3 (2.2)	3 (2.3)	6 (4.5)	2 (5.4)	2 (1.5)
Confidence interval (%)	0.0, 4.1	0.5, 6.3	0.5, 6.5	1.7, 9.5	0.7, 18.2	0.2, 5.4
Components of primary safety endpoint‡						
Fatal/critical bleeding, n (%)	0	0	0	0	0	0
Bleeding leading to reoperation, n (%)	0	2 (1.5)	2 (1.5)	0	0	0
Clinically overt bleeding leading to treatment cessation, n (%)	0	0	0	1 (0.7)	1 (2.7)	1 (0.8)
Clinically overt bleeding with a fall in hemoglobin, n (%)	0	1 (0.7)	1 (0.8)	3 (2.2)	1 (2.7)	2 (1.5)
Clinically overt bleeding leading to blood transfusion, n (%)	1 (0.8)	1 (0.7)	1 (0.8)	4 (3.0)	2 (5.4)	2 (1.5)
Bleeding site						
Surgical-site bleeds, n (%)‡	1 (0.8)	3 (2.2)	3 (2.3)	5 (3.7)	2 (5.4)	1 (0.8)
Extracutaneous-site bleeds, n (%)‡	0	0	0	2 (1.5)	0	1 (0.8)
Clinically relevant non-major bleeding, n (%)	2 (1.5)	8 (5.9)	3 (2.3)	6 (4.5)	1 (2.7)	0
Minor bleeding, n (%)	4 (3.0)	6 (4.4)	11 (8.3)	14 (10.4)	1 (2.7)	6 (4.5)

*Dose arm suspended because of regulatory request.

†Major, postoperative bleeding was defined as bleeding starting ≥6 h after surgery, or after the first postoperative dose of study medication (whichever came first), but not >2 days after the last administration of study drug.

‡Patients may have experienced more than one bleeding event, or a bleeding event that met the criteria for more than one bleeding classification.

	BAY 59-7939 b.i.d.					Enoxaparin once daily
	2.5 mg (n = 132)	5 mg (n = 136)	10 mg (n = 133)	20 mg (n = 134)	30 mg (n = 37)*	40 mg (n = 132)
Patients receiving blood transfusions, n (%)	74 (56.1)	77 (56.6)	78 (58.6)	89 (66.4)	24 (64.9)	77 (58.3)
Volume (mL; mean ± SD)	326 ± 355	314 ± 314	400 ± 441	451 ± 436	474 ± 517	350 ± 360
Patients with volume in drain (postoperative), n (%)	111 (84.1)	117 (86.0)	113 (85.0)	117 (87.3)	27 (73.0)	109 (82.6)
Volume (mL; mean ± SD)	545 ± 395	581 ± 470	640 ± 550	576 ± 594	481 ± 411	671 ± 1065

*Dose arm suspended because of regulatory request.

Table 3. Incidence and volume of blood transfusions, and incidence and volume of postoperative blood loss ($n = 704$; safety population)